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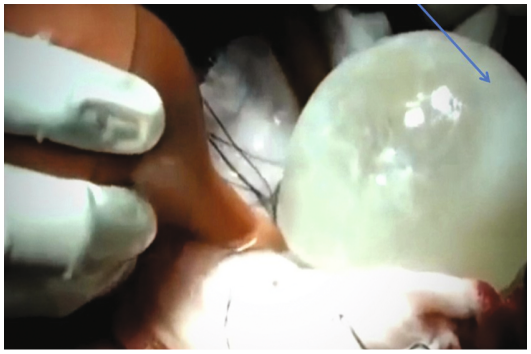

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Humanities

HIGHLIGHTS OF THIS ISSUE

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Indian Pediatrics Case Reports

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Contents

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Reflections

This is the last issue of 2022. We are about to complete 2 years of our existence. Things are falling into place: submissions are increasing, and the quality of articles has improved, but we still have a long way to go. I share some random thoughts that arose while preparing this issue.

The time for processing the manuscripts is taking longer than desirable. As Editor, I apologize to our authors for that. The delay occurs at various steps in the editorial process: with us – the editorial team; getting reviewers to accept the invitation and submit their comments within the stipulated timeline, and the author-reviewer/editorial team cycles required to refine the manuscript. We are working on this and hope that it improves. Till then, please bear with us.

Many clinicians do not submit cases that have not undergone genetic testing, presuming rejection. Having a confirmed genetic diagnosis definitely improves credibility. However, a well-worked-up case with corroborative clinical and laboratory evidence can be accepted sans genetic analysis, once the quality of writing becomes acceptable (i.e., the AAA syndrome). Similarly, some cases may be considered too mundane to merit publication (viz. tongue entrapment in a bottle), but they can provide a wealth of invaluable information to clinicians, who would remain oblivious regarding management unless they personally encounter such a case.

Then, we have cases that are more technically difficult to write about, like case series (which I touched upon in the previous issue) and referrals. Ask any resident – which patient is harder to present – the one who is medically naïve, i.e., without any antecedent visit to a facility; or the one who has bounced to – and – forth among doctors/hospitals; has undergone numerous tests; received multiple medication; and has minimal or no legible papers with documentation of events? The answer is obvious! The latter will be so convoluted that even, if you do manage to figure out what transpired during the patients' medical journey; converting the child's/parents narrative into a structured medical history, and presenting it in a logical and lucid manner is another major challenge in itself. It becomes an equally tough proposition for author/editor alike while writing/processing such a manuscript. On one hand, you have to respect the rules of the game, yet on the other, you also have to bend them a bit. The one-size-fits-all formula that works in nonreferred cases does not apply here. Much more work is required, including the number of editorial cycles required during manuscript processing.

The reason for highlighting these issues is because we view all our readers as potential authors. So when you read each case, do not simply appreciate the author's brilliant clinical approach used to arrive at the diagnosis, but also reflect on the subtle nuances employed in its presentation. After sieving through all the clinical information, the trick is to strike a balance between describing the salient positive and negative medical history and examination findings (sufficient enough to allow the reader to process them and consider potential diagnoses); while avoiding repetition and irrelevant details. In this issue, we have published five referrals; Wilke's syndrome, triple A syndrome, recurrent pleural effusion, cutaneous tuberculosis, and the radiology rounds. We would also like you to focus on the case series that we started publishing this year. Looking forward to some masterpieces for our upcoming issues in 2023. Happy New Year!

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Conflicts of interest

There are no conflicts of interest.

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Unilateral Acute Parotitis: A Novel Manifestation of Pediatric Coronavirus Disease

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Abstract

Background: Severe acute respiratory virus coronavirus-2 infection or coronavirus disease (COVID) is categorized into acute illness and late multiinflammatory syndrome in children (MISC). This has recently been challenged with recognition of presentations with mucocutaneous-enteric symptoms that display considerable overlap between the two. We recognized a similar overlap of manifestations when encountered the three cases of fever associated with unilateral parotitis. **Clinical Description:** The three patients were of different age groups ranging from 2 months to 7 years of age, all of whom presented with fever, unilateral swelling of face and neck consistent with the region of the parotid gland, and absence of other localizing symptoms or abnormalities on examination. All of them were positive for COVID antibodies, had negative COVID real-time polymerase chain reaction test, did not satisfy the diagnostic criteria of MISC, but had raised inflammatory markers. Since the workup for other common causes of acute parotitis was negative, a clinical diagnosis of post-COVID immune-mediated acute parotitis was kept. **Management:** All the three patients were managed with systemic steroids (oral or parenteral) and showed complete resolution of symptoms and normalization of laboratory parameters within a few days, a therapeutic response in alignment with an immune-mediated phenomenon. **Conclusion:** Acute unilateral parotitis with pyrexia may be a hitherto unreported late post-COVID manifestation that is immune mediated and shows an excellent therapeutic response to a short course of steroids.

Keywords: Multi-inflammatory syndrome in children, parotid swelling, steroids

Facts that have emerged since the onset of the pandemic regarding pediatric severe acute respiratory syndrome coronavirus-2 (SARS COV-2) infections are that children are usually only mildly affected, have low contagiousness, and rarely develop complications.[1] In most cases, the symptoms resemble other respiratory viral illnesses and tend to subside quickly, with only a minority requiring hospitalization.[2] A few months into the pandemic, the association of a multisystemic illness similar to Kawasaki disease with SARS COV-2 was recognized, which resulted in high morbidity and sparked apprehension regarding the long-term sequelae.[3] Multiinflammatory syndrome in children (MISC) has since become a familiar entity, with cases being reported from worldwide.[4,5] Mucocutaneous involvement with rash, conjunctivitis, and lymphadenopathy has been reported with acute infection as well as MISC.[6] Other rarer conditions associated with coronavirus disease (COVID) include acute disseminated encephalomyelitis, Guillain − Barre Syndrome, arthritis, intussusseception, relapses of nephrotic syndrome, etc.

We present three children with febrile illnesses with acute unilateral parotitis. The differential diagnoses for this clinical phenotype would usually include infectious parotitis, sialolithiasis, salivary gland abscess, and neoplasm. The reason for discussing this case series is to highlight the common factors that we noted in these children, all of whom presenting to our institute shortly after the peak of the third wave of COVID in February 2022. This included a positive COVID serology, negative real-time polymerase chain reaction (RT-PCR), raised inflammatory markers, and no other typical clinical manifestations of MISC. Although a few similar cases have been reported from other parts of the world, to the best of our knowledge, there are none from India.[7-9]

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Case 1

Clinical description

A 7-year-old girl presented to the emergency department with left-sided painless facial swelling near the angle of her jaw for

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the last 2 days, severe enough to cause partial malocclusion and trismus. This had resulted in difficulties in biting and chewing her food leading to decreased oral intake. There was no history of fever or rash during the current episode and she otherwise appeared well. There was no history of dental pain, swelling at any other site, conjunctival congestion or sudden appearance of facial asymmetry associated with weakness. There was no history of contact with similar patients or any such swelling in the past. There was significant past history of being diagnosed with coronavirus disease-19 on the basis of nasopharyngeal swab for RT-PCR when she had developed fever and upper respiratory tract symptoms 4 weeks before the current illness. The child had become asymptomatic and the RT-PCR had become negative within 7 days. There was a history of fever with upper respiratory symptoms in two other family members, but none of them had undergone COVID RT-PCR at that time and had shown full recovery. There was no similar illness in the past. The child had been immunized including mumps vaccine as part of MMR vaccine, studied in class 2nd, and had no other contributory history.

On examination, the patient was afebrile and her vitals were stable. Her body mass index was within the normal limits for her age. She had a visible swelling of the left cheek and adjoining preauricular and submandibular areas which measured approximately 7 cm × 5 cm. The swelling was firm, nontender and did not localized increase in temperature, erythema, induration, or fluctuation. The intraoral examination was normal, with no purulent drainage expressible from Stensen's duct, dental caries, or gingivitis. There was no conjunctival congestion, redness of tongue, rashes, or lymphadenopathy. Respiratory, cardiovascular, abdominal, and neurological examinations were noncontributory. On the basis of history and examination, the differential diagnoses considered were mumps, parotid gland abscess, sialolithiasis, and juvenile recurrent parotitis. The absence of prodromal symptoms, being vaccinated, and the nontender and nonerythematous nature of swelling made mumps as unlikely. Similarly, the absence of toxicity and fluctuation precluded suppuration. Juvenile recurrent parotitis has a similar phenotype but has to be recurrent. Investigations were planned keeping these differentials in mind.

Management and outcome

Initial investigations were planned to determine the anatomical origin of the swelling, and laboratory evidence of infection or inflammation. Local soft-tissue ultrasonography demonstrated diffuse asymmetric enlargement and swelling of the left parotid gland without any evidence of an obstructing stone, mass, or abscess. Multiple enlarged lymph nodes were noted in the intraparotid and retroparotid areas. Laboratory values showed normal blood counts, but raised inflammatory markers including raised C-reactive protein (CRP) 33 mg/L and raised erythrocyte sedimentation rate (ESR) 30 mm/1st h. Serum amylase was also raised at 250 U/L (normal 40–140 U/L). A repeat COVID RT-PCR that was negative ruled out re-infection. SARS-CoV2 immunoglobulin G antibodies were elevated (31 AU/ml; normal <10 AU/ml). Investigations to assess the extent of systemic inflammation due to COVID revealed normal D-Dimer (0.27; normal <0.50 ug/ml) and serum ferritin (45; normal 13–150 ng/ml) levels.

Based on the clinical features of a nonsuppurative swelling of the parotid gland with no other associated symptoms, recent history of COVID, presence of anti-COVID antibodies along with elevated CRP and ESR suggested it to be a post-COVID complication which was probably immune mediated. The absence of other clinical features such as fever, rash, and other systemic involvement and normal levels of D Dimer and serum ferritin excluded the diagnosis of MISC.

The patient had been started on oral amoxycillin at admission but showed no response after 3 days. With the absence of an alternate diagnosis, the possibility of an immune mediated post-COVID parotitis was considered and she was started on oral prednisolone (1 mg/kg/day). She showed rapid resolution of swelling which almost completely disappeared by the 5th day. A repeat CRP done on the same day was normal (4 mg/l), and the steroids were stopped.

Case 2

Clinical description

A 3.5-year-boy presented with fever and swelling of the right angle of his jaw for 3 days. The fever was mild grade. There was a history of poor appetite for the same duration. There was no history of cough, cold, rashes, loose motions, fast breathing, or swelling at any other site. There was no history of any febrile illness in the recent past, or of having mumps. There was no history of fever in any family member. He was completely immunized as per the schedule.

The patient was febrile (temperature 37.9°C) and had stable vitals. His anthropometric parameters were within the normal range for his age. Mild pallor was observed. The swelling in the right angle of the jaw was approximately 8 cm × 5 cm, firm, nontender, and nonfluctuant. The examination of the oral cavity did not reveal any caries or discharge from stensens duct. There was no rash, lymphadenopathy, redness of the conjunctiva, or tongue. There was no testicular swelling. There were no other pertinent findings on systemic examination.

Management and outcome

As the patient was hemodynamically stable and nontoxic at the time of presentation, a watch and wait policy was adopted and oral paracetamol prescribed, while we awaited the test results. The patient became afebrile on the 2nd day of admission, but the swelling remained the same size.

His laboratory parameters revealed leucocytosis (17400 × 10^9/L) which was predominantly lymphocytic. ESR was increased (44 mm) but CRP normal (5 mg/L). Immunoglobulin G antibodies for mumps were negative. The COVID RT-PCR was negative but serology for antiCOVID antibodies was positive (40.75 AU/ml). Ultrasound of the parotid showed a bulky right parotid with patchy hypoechoic areas within the parenchyma suggestive of parotitis. As there were no other

Table 1: Demographic and clinical features of the three patients of COVID associated parotitis

Age/sex	Clinical features	Features in favour of MISC	Features against MISC
7 years/ girl	Anorexia Unilateral parotid swelling	SARS anti-COV-2 antibody positive Increased CRP, ESR	Absence of fever, rash, and any systemic involvement
3.5 years/ girl	Fever Unilateral parotid swelling	Fever SARS anti-COV-2 antibody positive Increased ESR and leucocytosis	Absence of rash and any systemic involvement
2 months/ boy	Fever Irritability, unilateral parotid swelling	Fever SARS anti-COV-2 antibody positive Increased CRP, ESR, D-dimer, and leucocytosis	Absence of rash and any systemic involvement

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, MISC: Multi inflammatory syndrome in children, SARS: Severe acute respiratory syndrome

clinical features suggestive of MISC including fever, rash, lymphadenopathy, or systemic involvement, the patient was not further evaluated on the lines of MISC. In view of persistence of swelling even after 5 days, the possibility of a parotid swelling secondary to an immune-mediated phenomenon was kept and patient initiated on low dose oral prednisolone (1 mg/kg/day). Like the first case, there was good therapeutic response and almost the complete resolution of the swelling by the 5th day.

Case 3

Clinical description

A 2-month-old boy presented with fever for 5 days, a swelling on the right side of his face (near the angle of his jaw), irritability, and decreased breastfeeding for 2 days. There was no history of cough, cold, or difficulty in breathing before or during this illness. There was no history of loose motions, vomiting, rash, lethargy, or seizures. He was passing urine normally. There was a history of a brief febrile illness associated with cold and cough, in two family members including his mother a month earlier. They had not been investigated, but had recovered within 5 days. The baby had remained asymptomatic at that time. He was an exclusively breastfed infant. Both the antenatal and perinatal periods had been uneventful. He had received his immunization at 1.5 months.

On examination, the infant was febrile (temperature 38°C), irritable, and had no dehydration or abnormal vital signs. The anterior fontanelle was at level. The swelling present near his right angle of the jaw was around 5 cm × 4 cm in size. It was firm to palpate and there was no fluctuation, tenderness, or erythema. The examination of the oral cavity was normal. There was no abdominal tenderness or any testicular swelling. No abnormality was detected on systemic examination.

Management and outcome

Keeping in view the age of the baby and presence of fever, the patient was initially investigated and treated on the lines of sepsis. On complete blood count, there was leukocytosis (18,700 × 10^9/L) with normal platelet count (2,50,000 × 10^9/L). The CRP level was raised at 28 mg/dl (normal 0–6 mg/l). Nonetheless, in view of the pandemic and recent history of fever in the family, he was investigated for COVID. Although the COVID RT-PCR was negative, anti COVID antibodies were significantly raised (58.96 BAU/ml). Further investigations on the lines of MISC revealed raised d-dimer levels at 1260 ng/ml, but serum ferritin (75.78 ng/ml) and pro thrombin index level (INR 100%) were normal. The ultrasound of the right parotid gland revealed enlargement of the gland with few sub-centrimetric lymph nodes underneath, and no obstruction to the drainage. Echocardiography was normal with normal calibre coronaries. The patient had been started on broad-spectrum antibiotics at admission. The possibility of MISC was reviewed considering the fever, positive anti SARS COV 2 antibodies and raised inflammatory markers, but there were insufficient criteria to meet the case definition. Considering post-COVID parotitis, the patient was started on IV methylprednisolone at 2 mg/kg/day. He became afebrile within 48 h and there was complete resolution of the swelling by day 5. Repeat investigations showed a normal TLC (7500 × 10^9/L) and a normal CRP level (6 mg/l). Steroids were stopped.

Discussion

SARS COV-2 has been characterized into two distinct clinical phenotypes, namely an acute COVID phase in which the case is PCR positive and MISC in which the patient has a association with COVID and are positive for COVID antibodies. The WHO has published a criteria for the diagnosis of MISC, which in addition to fever requires the presence of involvement of two or more organ systems and laboratory evidence of inflammation. This characterization of pediatric COVID into acute and postinfectious entities has recently been challenged as there is the significant overlap between both.[6] There have been children meeting the criteria for MIS-C in both the acute phase of infection (polymerase chain reaction positive) and postacute or convalescent phase of infection (antibody positive) groups.[6] Whereas the acute group presented more commonly with respiratory symptoms, the postacute or antibody-positive group presented with muco-enteric symptoms.[6] Being a pro-inflammatory condition, MISC results in inflammation of various body organs such as the skin, lymph nodes, and heart tissue. The affected tissues show infiltration of T cells, and B cells with the presence of microthrombi, indicative of an ongoing anti-viral immune response and microangiopathic damage, respectively.[10] However, there is still no clear understanding why certain tissues of the body are more predisposed to viral propagation and whether this depends on the strength of the local immune response.

Shortly, after the peak of the third wave of COVID in February 2022, we encountered these three cases of various ages with fever and unilateral parotid swelling. The fact that all these children were negative for COVID PCR, positive for COVID antibodies, had elevated pro-inflammatory markers, but did not satisfy the MISC criteria [Table 1], suggested post-COVID immune mediated parotitis, rather than an acute infection. There was the absence of a temporally related viral illness in two of the patients preceding the parotid swelling, but it is well known that acute COVID infection can be asymptomatic and hence go unnoticed. The youngest of our patients was only 2 months old at presentation. Only a few cases of parotitis have been reported in young infants, most of which are due to bacterial suppuration.[11] We ensured that the common causes of acute unilateral parotitis such as mumps and acute suppuration were excluded, before starting the short course of steroids. The excellent therapeutic response (complete resolution of symptoms and normalization of inflammatory biomarkers) that was observed to this brief immunosuppression is another point in favor of an immune-mediated condition.

Recently, there have been a few reports of COVID-associated parotitis in adults[7] and a case series of 15 patients which had two children aged 10 and 13 years.[8] Although the direct spread of SARS CoV-2 into the parotid tissue is theoretically possible due to the presence of angiotensin-converting enzyme 2 (the virus receptor) in the parotid tissue, the exact mechanism of parotid enlargement is still not understood.[12] In one of the case reports, based on the MRIs of parotid gland, it was suggested that there is the presence of adenitis, which might impair the gland functioning and block the main gland duct (Stenon's duct), leading to saliva retention and parotid tissue inflammation.[13] The ultrasound studies of our patients reveal a similar picture with enlargement of intraparotid lymph nodes as well as parotid gland. This enlargement of the parotid gland has itself been hypothesized due to lymphadenitis being a causal factor. A fundamental difference between previous reports and our case series is that in the former, all the patients were adults who were SARS COV-2 positive at presentation, while our patients were children with negative RT-PCR for SARS COV-2 but positive for anti-COVID antibodies. This suggested that the parotitis in these children was a late manifestation which could be immune in origin, not vastly different in the pathogenesis from MISC.

Each patient was treated individually by separate clinicians in the department before the dots were connected. That is the reason for variation in the spectrum of inflammatory markers and type of immunosuppression used, as there is no existing standard protocol. Another reason for dissemination these clinical details and our hypothesis is to trigger research interest. Studies can be designed to explore this phenomenon further to ascertain the relation of SARS COV 2 with acute parotitis in which a complete inflammatory marker profile, viral panel, and parotid gland magnetic resonance imaging, functioning, and histopathology can be included in the work-up.

Lessons learnt

- Acute parotitis in infants and children can be a late manifestation of COVID infection
- The fact that these children were negative for COVID PCR, positive for COVID antibodies, had elevated pro-inflammatory markers, and displayed therapeutic response to steroids suggested post-COVID immune-mediated parotitis, rather than acute infection
- In the setting of the pandemic, a high index of suspicion for COVID related acute or late infection should be considered in patients with unusual manifestations, in whom other etiologies cannot be found.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

An Unusual Case of Tongue Entrapment in a Plastic Water Bottle

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Abstract

Background: Foreign bodies inside the oral cavity are commonly encountered among children. One peculiar occurrence is when the tongue gets entrapped in foreign bodies such as bottles. This happens as children often insert their tongues into the bottle and apply oral suction to ingest the last few drops from the bottle. There is a paucity of data in Indian literature and no recommended guidelines for the management of such cases. **Clinical Description:** The patient, a 12-year-old boy had a history of inability to remove a plastic water bottle sipper from around the tongue while swallowing water quickly. He was initially asymptomatic and then he started developing progressive pain and swelling on the anterior part of the tongue. On examination, the plastic sipper was constricting the tongue circumferentially and the patient felt a sharp pain on maneuvering the bottle. Minimal discoloration of the anterior part of the tongue had set in 1 h after the presentation. **Management:** Lubrication with 2% lignocaine jelly and ice packs circumferentially followed by attempts of gentle traction and manipulation to remove the foreign body were unsuccessful. Consequently, the patient was shifted to the emergency operation theater where the patient was sedated with intravenous (IV) ketamine and midazolam after securing a nasopharyngeal airway with 100% preoxygenation. An orthopedic bone cutter was used, and a radial cut was given on the impacted end of the bottle, and the constricted part was removed as pressure on the tongue was released, followed by 100% oxygenation with bag and mask ventilation. **Conclusion:** Immediate intervention in cases of the entrapped tongue can prevent grave consequences such as airway compromise and tongue ischemia and necrosis. Mechanical removal can be done safely using heavy scissors or orthopedic bone under IV sedation after securing the airway in collaboration with the anesthesia team.

Keywords: Deep sedation, foreign bodies, mouth, surgical instruments

Foreign bodies inside the oral cavity are commonly encountered among the pediatric population. One peculiar occurrence is when young children present to the emergency department with tongue entrapment in foreign bodies, especially water bottles, glass, aluminum, metal, plastic, and codd-necks (with marbles within).[1] This happens when children insert their tongues into the bottle and apply oral suction to ingest the last few drops from the bottle. There are no recommended guidelines on the management of these cases. Crucial factors to consider include the duration of entrapment, amount of edema and congestion of the tongue, general condition of the patient, potential risk of airway compromise, and availability of resources. A variety of novel, innovative techniques are usually attempted. These start with gentle traction, traction with lubrication, and positive pressure technique, and may escalate to the use of dental drills, orthopedic wire cutters, surgical scissors, and the Gigli saw wire to remove the constricting foreign body.

We present this particular patient to create awareness of this underreported emergency and highlight the challenges we faced due to delayed presentation, administration of anesthesia, and planning surgical intervention.

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Clinical Description

A 9-year-old boy presented to the ENT emergency with the inability to remove a plastic water bottle sipper that had got stuck around his tongue. The patient had a history of drinking water from a plastic water bottle approximately 4 h before the presentation. While swallowing water quickly, the patient felt his tongue being pulled inside and was unable to withdraw it on pulling back or applying pressure. Initially, he was asymptomatic, then he started developing pain and perceived that the anterior part of his tongue appeared to be progressively swelling up. There was no history of any bleeding into the oral cavity or discoloration of the tongue.

The child was very anxious and apprehensive on the presentation and the parents though worried, remained calm,

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and cooperative. There was no history of any similar events in the past. The developmental history was normal without any behavioral issues, pica, or atypical repetitive oral habits. He was an average student studying in class six.

The child was made to comfortably lie on the table in the examination room. His temperature was 37°C, pulse rate –85 beats per min, capillary filling time –<3 s, blood pressure –110/65 mm Hg (50th percentile, Indian Academy of Pediatrics Growth Charts), and respiratory rate –18 breaths per min with the saturation of peripheral oxygen (SpO2) of 99% in room air. His body mass index was 19.3 kg/m^2 (71st percentile, Indian Academy of Pediatrics Charts). There was no pallor, cyanosis, or facial congestion. On examination of the oral cavity, a black water bottle sipper was seen constricting the tongue circumferentially. The protruding anterior part of the tongue was congested and edematous. There were no abrasions, lacerations, or any active bleeding [Figure 1]. The rest of the general physical examination was within normal limits, and the systemic examination was not contributory.

Management and outcome

The parents and child were reassured. The part of the bottle not involving the tongue was removed using heavy scissors. The patient experienced sharp pain while maneuvering the bottle for which he was administered intravenous (IV) paracetamol. The stuck end of the bottle was lubricated with 2% lignocaine jelly circumferentially and ice packs were applied on the protruding part and the region of constriction of the tongue to decrease the congestion. We tried to remove the bottle by gentle manipulation but failed due to the pain and discomfort experienced by the patient. Minimal discoloration of the anterior part of the tongue had become apparent by now.

IV dexamethasone (3 mg) was administered to decrease inflammation and edema, and the patient was shifted to the emergency operation theater. High-risk consent was taken by the anesthesia team in view of anticipated difficulties in securing the airway. The patient was secured with a nasopharyngeal airway and preoxygenated with 100% oxygen. Following this, he was sedated with IV ketamine (20 mg), midazolam (1 mg), and fentanyl (30 µg). Oxygenation was continued through the nasopharyngeal airway. The orotracheal intubation in this patient was difficult, so measures for an emergency tracheotomy were kept on standby just in case there was any difficulty in ventilating the patient. However, he continued to maintain SpO2 of 98% through the nasopharyngeal airway, and therefore, a tracheostomy was not required.

An orthopedic bone cutter was used to give a radial cut on the impacted end of the bottle [Figure 2]. The pressure on the tongue was released and the bottle was removed. Postremoval of the foreign body, the patient was observed for 15 min to look for any signs of airway obstruction. There was no obstruction of the airway by the slightly swollen tongue. Now, the tongue could be closely inspected. Apart from the edema, congestion, and mild discoloration of the anterior part of the tongue that had been impacted, there was no evidence of any abrasions, lacerations, or bleeding points [Figure 3a]. The patient was able to protrude his tongue but experienced mild pain while doing so. The discoloration of the tongue gradually subsided by the 2nd postoperative day [Figure 3b], and the patient was

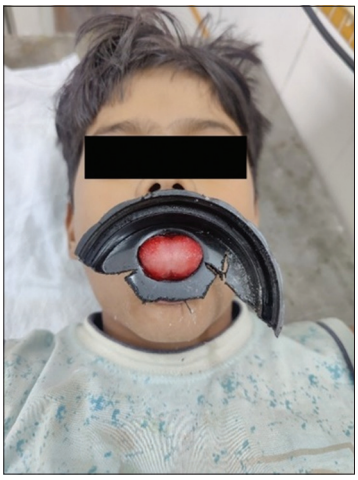

Figure 1: Tongue entrapped in water bottle plastic sipper

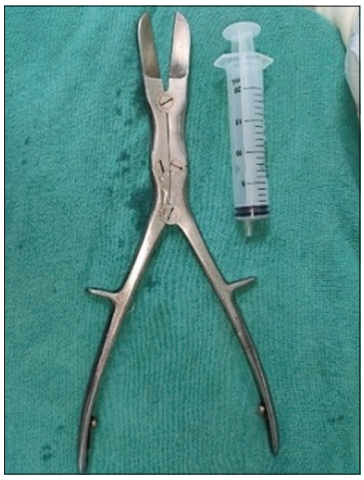

Figure 2: Orthopedic bone cutter used to cut the impacted foreign body

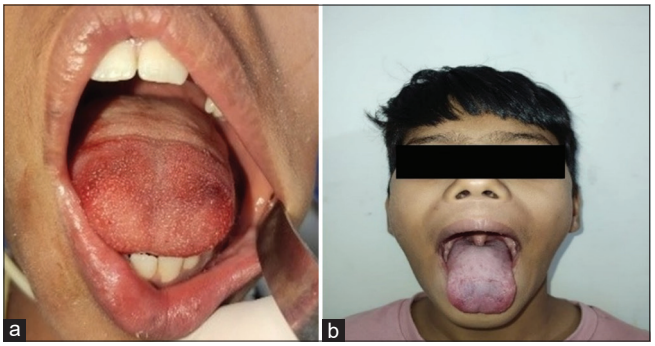

Figure 3: (a) Intraoperative appearance, (b) Postoperative appearance after foreign body removal

Table 1: Comparison of management and outcomes of cases of tongue entrapment in foreign bodies

Study	Age/sex	Presentation	Duration	Strategy used	Outcome
Singh, *et al*.[9]	9 years/male	Tongue tightly entrapped inside plastic bottle neck; tongue hemangiomas; intellectual disability	Unknown	Gigli saw wire	Successful removal, no injury/ postprocedure complications
Current study (index case)	12 years/male	Tongue entrapped in plastic water bottle sipper; tongue edematous, firm, and tender	4 h	Orthopedic bone cutter	Successful removal, no injury/ postprocedure complications

discharged and kept under follow-up. He remained well when seen after 1, 2, and 8 weeks.

Discussion

The lodgment of foreign bodies in children is a common scenario, but reports of tongue entrapment in bottles are relatively uncommon. Children drink from rigid bottles which sustain negative pressures.[2] Sometimes, the tongue gets entrapped within the lumen of the bottle when it remains for a slightly longer period during which a vacuum is created. This causes tongue edema and subsequent strangulation of the tongue. Immediate intervention in cases of the entrapped tongue can prevent grave consequences such as airway compromise and tongue ischemia. If there is a delay in removal beyond 4 h as was seen in a case of tongue trapped in the lid of a plastic drinking bottle, venous congestion can occur and lead to tip necrosis.[3] Staying calm throughout the episode is very important. In this case, the patient was made to lie comfortably and advised to lay still, appropriate analgesia was given both locally and intravenously to alleviate the pain. The parents were counseled of the nature of the condition, the nature of the surgery, and the risks and complications associated with the procedure and in the postoperative period.

There is a paucity of published cases of tongue entrapment in Indian settings. Details of an earlier case are given in Table 1 and compared with the present case. Similar cases have been reported in scientific literature, in which different approaches have been described. Removal can be safely done under sedation, but with anesthetic backup. The authors have described the use of various sedation and presurgical topical or general anesthesia. Topical anesthesia using 2% lignocaine jelly can be applied at the junction of the tongue and point of constriction, as was done in this case. Once the patient is shifted to the operation theater, the patient can be sedated using IV dissociative anesthetic drugs such as ketamine and short-acting benzodiazepines such as midazolam along with IV analgesics. In most cases, the glass, plastic, or metal bottles had to be physically cut to relieve the entrapped tongue. Mills and Simon successfully managed to release an entrapped tongue by positive pressure technique, in which a feeding tube was advanced between the tongue and the bottleneck into the bottle and 240 ml of air was pumped into the bottle with a 6 ml syringe following which the tongue retracted from the bottle, slowly at first, and then suddenly.[4] In another case, the tongue entrapped in a glass bottle was successfully released using a Rongeur and Mallet.[5] There are reports of the use of heavy instruments such as orthopedic wire cutters, tin snips, ring cutters, and heavy scissors (to release the tongue by cutting the constricting part) and the Gigli saw to release the entrapped tongue by threading the wire between the tongue and the constricting object and using the handles to cut the constricting part radially at that point.[6-9] The use of a surgical drill to release the organ from plastic bottles has also been described.[3,10] The risks during the removal of foreign body from the tongue include loss of airway, pulmonary aspiration, and tongue ischemia. The patient should be closely monitored postoperatively as tongue swelling can lead to respiratory distress and an airway emergency. Most children complained of edema, discoloration, and pain postoperatively but eventually made full recovery.

To conclude, parents should be made aware of this unusual but dangerous condition related to water bottles. It calls for preemptive parental counseling, in which children can be taught not to attempt to drink the last few drops from the bottle, to drink slowly, and not to suck vigorously at the bottle sipper.

Declaration of patient consent

The authors certify that they have obtained the appropriate consent from the parent. The legal guardian has given his consent for the images and other clinical information to be reported in the journal. The guardian understands that the name and initials will not be published, and due efforts have been made to conceal the same, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Leukemic Optic Neuropathy: A Harbinger of Relapse in Acute Lymphoblastic Leukemia

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Abstract

Background: Leukemic infiltration of the optic nerve is a neuro-oncologic emergency and also a sign of extramedullary central nervous system relapse. It presents a clinical dilemma in the early stages due to multiple differentials. Patients with leukemia receive radiation and chemotherapy are thus, susceptible to inflammatory, toxic, and infectious causes of optic neuropathy, besides infiltration with tumor cells. **Clinical Description:** A 15-year-old boy treated for acute lymphoblastic leukemia (ALL) and in remission for 7 months, presented with the unilateral decreased vision for 7 days. A structured evaluation was done, comprising visual acuity, color vision, field of vision, fundus, ophthalmoscopy, ultrasound b-scan, and magnetic resonance imaging of the orbit. The final diagnosis was leukemic infiltration of the optic nerve. Cerebrospinal fluid (CSF) analysis confirmed the presence of atypical lymphocytes. **Management:** The patient was diagnosed with extramedullary relapse of ALL. Since there are no standard guidelines, a literature review was performed, and the treating team decided to start the patient on stand-alone chemotherapy. Symptomatic resolution became apparent within 10 days. On follow-up, the optic nerve lesion resolved with residual gliosis in the surrounding retina. The CSF has become clear, and the patient is now considered to be in remission. **Conclusion:** It is important to use a structured clinical approach coupled with investigations to recognize the ocular involvement of ALL (especially in younger patients). There is a need for a regular routine ophthalmological examination in patients in remission for early detection of a relapse. There is a strong felt need for pediatric hemato-oncologists to plan research in this area to generate data so that recommendations for the management of extramedullary relapses are formulated.

Keywords: Central nervous system metastasis, leukemia, optic nerve metastasis, optic neuropathy

Acute lymphoblastic leukemia (ALL) is a malignancy of B- or T-lymphoblasts characterized by uncontrolled proliferation of abnormal, immature lymphocytes and their progenitors. The replacement of typical cellular components of bone marrow and other lymphoid organs with atypical cells results in the typical manifestations of ALL.[1] These include progressive pallor, petechiae, purpura, generalized lymphadenopathy, and hepatosplenomegaly.

The relapse of ALL in ocular tissues and the central nervous system (CNS) is rare and poses a diagnostic and therapeutic challenge. Due to its rarity, there are no standard guidelines and treatment is generally guided by previous case reports.[2,3] Leukemic infiltration of the optic nerve is considered an emergency that requires an immediate initiation of therapy, including corticosteroids, chemotherapy, and/or radiation.[4]

We present a case of cerebrospinal fluid (CSF)-proven, isolated, CNS relapse of ALL, in which optic nerve infiltration was the first and sole manifestation. There was a complete resolution of the optic nerve infiltration and remission of the ALL with chemotherapy alone.

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Clinical Description

A 15-year-old boy, who was a follow-up case of ALL under treatment presented in the seventh month of remission with the blurring of vision of the right eye and headache for 7 days. The blurred vision was not associated with any ocular pain, congestion, discharge, lesions, foreign body sensation, or preceding trauma. The headache was severe, generalized, and not associated with projectile vomiting or any diurnal variation. There was no history of fever, fatigue, bony pains, rash, or bleeding for any site. Appetite was unaffected. There was a significant history of his receiving chemotherapy as per the ALL-Berlin-Frankfurt-Munich 90 protocol (BFM90),

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as depicted in Figure 1.[5] The child was off treatment from 6 months when he presented with the aforementioned symptoms.

The vital parameters at the time of examination were heart rate of 98/min, respiratory rate of 22/min, the temperature of 98.40F, and blood pressure of 110/70 mm Hg (right upper limb, supine position), all of which were normal. The child's weight was 34 kg (on 3rd centile), height 143 cm (<3rd centile), and body mass index was 16.6 kg/m^2. There was no pallor, icterus, cyanosis, clubbing, edema, or lymphadenopathy. The testicular examination was normal. The child was conscious, cooperative, and oriented to time, place, and person. The cranial nerve examination did not reveal any involvement except for an absent pupillary reflex on the right side. The sensory and motor system examination was unremarkable. There were no meningeal signs. No additional systemic findings could be documented on the respiratory, cardiovascular, and abdominal examinations.

On structured ocular examination, the visual acuity was 20/60 in the right eye and 20/20 in the left eye. There was no restriction of the ocular motility, and there was no anisocoria, but there was a relative afferent pupillary defect in the right eye. Color vision was also impaired in the right eye, but the confrontation fields were normal. On fundus examination, a large mass lesion measuring 5mm × 4 mm × 2mm with telangiectatic vessels and surrounding splinter hemorrhage in the inferotemporal region was seen in the right eye [Figure 2a]. The left eye was normal. An ultrasound B-scan of the eye was planned, which revealed a dome-shaped homogeneous lesion with medium reflectivity over the optic disc in the right eye [Figure 3a]. These ocular findings were consistent with a diagnosis of optic nerve infiltration secondary to leukemic cells. The clinical implications were a relapse, and further investigations were planned accordingly.

A complete hemogram revealed predominantly normocytic normochromic red blood cells with no immature cells. The bone marrow biopsy showed a hypocellular marrow exhibiting normal morphology and maturation of all hematopoietic elements with no minimal residual disease.

Contrast-enhanced magnetic resonance imaging of the brain and orbit revealed thickened enhancing multiple cranial nerves and infiltration at the level of optic disc on the right side [Figure 3b]. CSF examination identified malignant cells, thus confirming extramedullary relapse. The patient was classified as extramedullary early relapse (reinduction phase-intermediate risk) and was started on chemotherapy according to the UK ALL R3 protocol.[6]

There was improvement in vision and resolution of headache by day 10 posttreatment. He was discharged and kept under a close follow-up. At the 6-month visit, his visual acuity has improved to 20/30, the fundus examination showed a complete regression of the optic disc lesion with the presence of refractile bodies inferior to the optic disc, and the residual gliotic retinal changes in the area of the tumor [Figure 2b]. Subsequent CSF serial analysis was free of malignant cells.

Discussion

Leukemic infiltration of the optic nerve is a neuro-oncologic emergency and a sign of extramedullary CNS relapse. It is uncommon and presents a clinical dilemma in the early stages since it may mimic other etiologies, besides nerve infiltration with tumor cells. Since patients with leukemia are subjected to radiation and strong intravenous chemotherapeutic agents, they are susceptible to inflammatory, toxic, and infectious causes of optic neuropathy. Therefore, in such a setting, a detailed history and examination are invaluable in deciding the direction of the investigation. In our case, the presence of a large mass lesion made the diagnosis of leukemic infiltration quite obvious. However, it can be quite challenging in the early stages when the only sign is optic disc edema. Then, it becomes imperative to rule out the other probable causes of optic nerve infiltration.

An invasive intravitreal biopsy can also be done in cases of clinical suspicion of ocular involvement. A literature review by Myers *et al*.[4] showed that optic neuropathy was the initial presentation in only two of the 19 patients of ALL with infiltrative optic neuropathy, and eight had malignant cells in the CSF. Most of the previously published reports had a

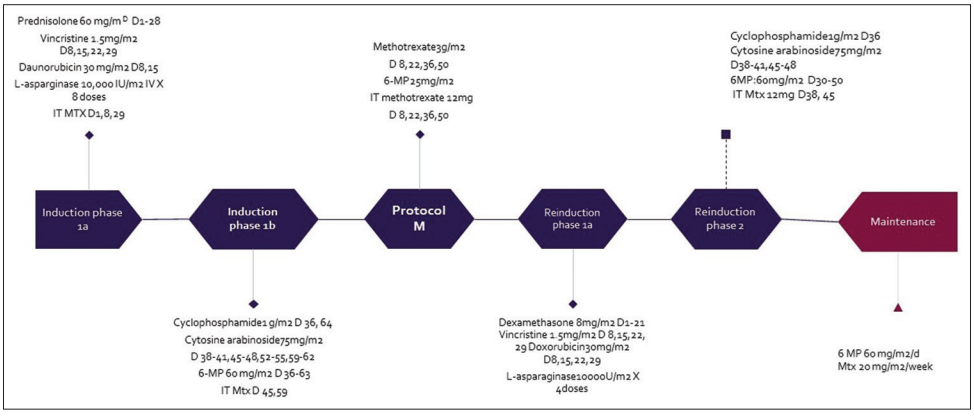

Figure 1: The ALL-Berlin-Frankfurt-Munich 90 protocol (BFM90) that the child received. ALL: Acute lymphoblastic leukemia

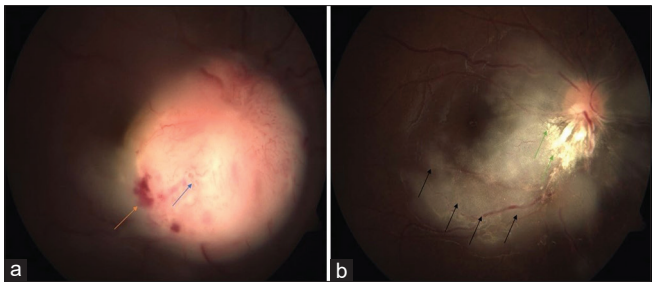

Figure 2: (a) Fundus image of the right eye showing a large mass lesion with surrounding telangiectatic vessels (blue arrow) and hemorrhage (orange arrow) in the inferotemporal region. (b) Postchemotherapy fundus picture showing regression of the optic disc lesion with the presence of refractile bodies inferior to the optic disc (green arrows) and the residual gliotic retinal changes in the area of the tumor (black arrows)

presumptive diagnosis of optic nerve infiltration, and a biopsy had been performed in only one case.

Another important aspect to consider is the age. In this case, the patient was old enough to express his visual impairment, but this might be missed in younger children with ALL. Isolated infiltrative optic neuropathy is most commonly seen in ALL and B-cell nonHodgkin's lymphoma (NHL), though it has also been reported with acute myeloid leukemia, chronic myelogenous leukemia, T-cell NHL, Hodgkin's lymphoma, and histiocytic lymphoma.[4,7]

Therefore, we suggest that all patients with leukemia must undergo a baseline ophthalmological examination and a repeat exam every 3 months, or earlier if any visual symptoms develop. A long-term follow-up study of patients in the remission phase of ALL can help establish standardized guidelines for follow-up and management of patients presenting with optic nerve infiltration. With respect to management, in four of the case reports reviewed by Myers *et al*., ALL patients with optic nerve involvement were treated with adjunct radiotherapy based on the hypothesis that drug delivery is limited across the blood-ocular barrier.[8-11] There were only two cases, besides ours, in which the patients with ocular involvement had recovered fully with chemotherapy alone.[12,13]

The aim of this report was to highlight the two aspects of the management of children with ALL, which may get overlooked if not actively sought. First, the importance of using a structured clinical approach coupled with investigations to recognize ocular involvement of ALL (especially in younger patients); and second, the need for a regular routine ophthalmological examination in patients in remission so that a relapse may be detected early. Obviously, the findings of a single case report or review cannot be generalized for the management of similar cases. There is a strong felt need for pediatric hemato-oncologists to plan cohort studies to identify patients at high risk of extramedullary relapse and generate data so that recommendations for management can come into existence.

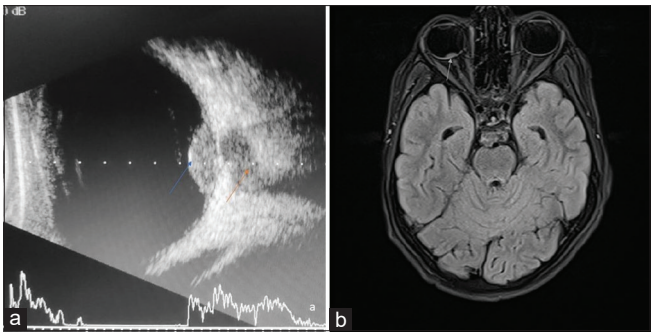

Figure 3: (a) Ultrasound B-scan axial view of the right eye showing a homogenous dome-shaped lesion with medium internal reflectivity, no posterior shadowing, lying over the optic disc (blue arrow; orange arrow pointing at the optic nerve). (b) A T1-weighted fat-suppressed axial MRI image or the brain and orbits showing a hyperintense lesion overlying the right optic disc associated with mild thickening of the right optic nerve (white arrow). MRI: magnetic resonance imaging

Lessons learnt

- Reduction in visual acuity can be a sole presentation of ALL relapse in the early stages
- ALL relapse in ocular tissues can be managed with stand-alone chemotherapy
- Further, long-term studies are required to establish guidelines for follow-up and management of patients presenting with ocular involvement.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Wolcott Rallison Syndrome: Beyond Neonatal Diabetes

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Abstract

Background: Wolcott–Rallison Syndrome (WRS) is a rare autosomal recessive disorder characterized by permanent neonatal diabetes mellitus, skeletal dysplasia, hepatic dysfunction, and other systemic associations. **Clinical Description:** A 3-month-old infant with a history of fever and poor oral intake presented with severe dehydration, acidosis and 3+ urine ketones and was diagnosed to have sepsis and diabetic ketoacidosis (DKA). He also developed acute kidney injury (AKI) with blood urea 118 mg/dL and serum creatinine 1.5 mg/dL. **Management:** The child was ventilated, stabilized, and managed for DKA with fluids and insulin as per guidelines. AKI was managed with peritoneal dialysis. Genetic analysis revealed homozygous mutation in eukaryotic translation initiation factor 2-alpha kinase 3 gene consistent with the diagnosis of WRS. A close follow-up was kept with regular screening for other associated manifestations. Central hypothyroidism was detected first followed by skeletal dysplasia and chronic kidney disease. Growth retardation and developmental delay are also present. **Conclusion:** Neonatal diabetes cases need an early genetic work up and watchful follow-up for the manifestation of other possible associated features.

Keywords: Central hypothyroidism, chronic kidney disease, neonatal diabetes mellitus, skeletal dysplasia

Presentation of diabetes in an infant younger than 6 months is known as neonatal diabetes, and it may be permanent or transient. In permanent diabetes, the condition persists throughout life whereas in transient neonatal diabetes, the condition remits within a year but may relapse in adolescence. Permanent neonatal diabetes occurs with a frequency of 1 in 90,000–1 in 210,000 live births,[1,2] some of which may be associated with genetic syndromes.

Neonatal diabetes is a monogenic disorder in which mutations have been identified at over a dozen genes/loci.[3] These include namely potassium channel J11, ATP-binding cassette transporter subfamily C member 8 (*ABCC8*), insulin (*INS*), 6q24, solute carrier family 2A2 (*SLC2A2*), *SLC19A2*, eukaryotic translation initiation factor 2 alpha kinase 3 (*EIF2AK3*), glucokinase, *Insulin* promotor factor 1, pancreas transcription factor 1 subunit alpha, and others. The genes involved in the syndromic forms of neonatal and infantile onset diabetes include Berardinelli-Seip congenital lipodystrophy 2 (*BSCL2*), *AGPAT2*, *SLC2A2*, and *EIF2AK3* genes. Consanguinity is an important factor in the syndromic forms. Understandably, genetic work-up is a very important component of the management of neonatal diabetes. The identification of the mutation not only has implications in genetic counseling, but also helps the treating physician in deciding therapeutic options, i.e., whether the need for insulin will be lifelong, or whether the patient can be managed with oral sulfonylureas.

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Wolcott-Rallison syndrome (WRS) is the most common form of neonatal diabetes in consanguineous pedigrees.[4] The various manifestations evolve over time and a regular follow-up is crucial for management. The outcome is usually unfavorable with death occurring by 2–3 years of age in most cases. In this report, we present an infant diagnosed with neonatal diabetes, identified with a mutation consistent with WRS and discuss the challenges that the family and we, the treating team, faced during a long and continuous 6 years' period of follow-up.

Clinical Description

A 3-month-old boy was brought to the emergency in an unresponsive state. On elicitation of history, it was found that the infant had high-grade fever that was present throughout the day for 6 days, associated with poor breast feeding. There was no history of cough, coryza, loose stools, vomiting, abdominal distension, or rashes in the initial course of illness. He had been

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taken for a medical consult and had been prescribed some oral medication, the nature of which was unknown and there was no written documents. He developed fast breathing in the last 2 days that was not associated with chest indrawing. The baby had stopped interacting with his mother for a few hours and became unresponsive which prompted his parents to rush to the emergency. There was no history of seizures, excessive crying, or paucity of movements of any part of the body. There was no history of bleeding from any site, fall, or trauma. He was passing urine normally, around 8 times a day.

There was no history of any similar episode in the past and the infant had had no significant illness since birth. He was born to a booked primi mother with an uneventful antenatal period. He was born by normal delivery at 38 weeks' gestation, with a birth weight of 2.5 kg and had displayed a smooth perinatal transition. At 3 months, he had been appropriately immunized and had attained milestones according to age. There was a history of consanguinity, his parents were first cousins. There was no history of diabetes mellitus or any significant medical illness in the family.

At admission, the infant had a temperature of 38°C, was tachypneic with a respiratory rate of 72/min (appearing acidotic in nature), and had tachycardia with a heart rate of 160 beats/min. The capillary filling time was 3 s, and peripheral pulses were palpable. He had features of severe dehydration with a depressed anterior fontanelle, dry mucosa, very slow skin recoil, and lethargy. Pallor was present. There was no icterus, cyanosis, or rash. His weight was 3.5 kg (Z score −4.65) and length was 56 (Z score −2.73). The sensorium was altered with a modified Glasgow Coma Scale of 7/15. There was no eye opening (E1), he was withdrawing limb to pain (M4) and moaning to pain (V2). The pupils were bilaterally equal, symmetrical and reactive to light**.** There was no focal neurological deficit. The abdomen was soft, nontender with the liver palpable 2 cm below costal margin. The respiratory and cardiovascular examination was normal.

Initial investigation in the emergency revealed a capillary blood glucose of 346 mg/dl and metabolic acidosis (pH 6.9 and HCO3 of 4.3 mEq/L) with a high anion gap. This prompted us to check the urine which revealed glycosuria and ketonuria (3+). He had a hemoglobin of 10.5 g/dL, elevated total leukocyte count of 24,000/mm^3, thrombocytosis (platelet count 742/mm^3), and raised C-reactive protein of 12 mg/L. The blood urea was 118 mg/dl, serum creatinine 1.5 mg/dl, serum sodium 136 mEq/L, and potassium 5.4 mEq/L. The liver function tests were normal. Since hyperglycemia, ketonuria, acidemia, and markers of infection were present, a diagnosis of diabetic ketoacidosis (DKA) with sepsis and possible meningoencephalitis was kept.

Management and outcome

In view of poor sensorium, acidosis, and severe dehydration, the infant was intubated and ventilated and shifted to the pediatric intensive care unit. He was administered 10% dehydration correction that was infused at a uniform rate over 48 h along with maintenance fluid as per guidelines of the International Society of Pediatric and Adolescent Diabetes.[5] Insulin was administered after the 1st h fluid bolus as an infusion of 0.1 unit/kg/hour. He was also given antibiotics and other supportive measures. The acidosis improved but did not resolve completely. The infant developed acute kidney injury; his blood urea increased to 129 mg/dl, serum creatinine rose to 2.1 mg/dL and urine output became low (0.5 ml/kg/h). Peritoneal dialysis was started that gradually resulted in a steady improvement in renal parameters, urine output and acidosis. A total of 129 cycles over 6 days were required and by day 7, the creatinine reduced to 0.9 mg/dl, the child had good urine output and got extubated. Insulin was gradually tapered to 0.05 unit/kg/hour with complete resolution of acidosis by day 4. The liver function tests and electrolytes remained normal. The blood culture was sterile.

Feeds were initiated along with a basal-bolus Insulin regime (regular Insulin thrice a day and isophane Insulin twice a day). An ultrasound revealed mildly increased kidney size with increased cortical echogenicity. Investigations directed toward the work-up of diabetes revealed a very high glycated hemoglobin (HbA1c) (11.6%), but the C peptide was negative. The onset of diabetes at an early age prompted us to seek an underlying genetic etiology. On sequence analysis of genes for neonatal diabetes (potassium channel J11, ABCC8, Insulin, and EIF2AK3), the child was found to be homozygous for an EIF2AK3 nonsense mutation, p.Tyr360Ter confirming the diagnosis of WRS. Further testing revealed that both parents were heterozygous for the same mutation.

At discharge, 23 days after admission, the blood glucose levels were well controlled on basal-bolus regime. The parents had been trained to care for the infant, check and record blood glucose, and in all the nuances of Insulin dosing and administration. They underwent genetic counseling in which they were explained the nature of the syndrome, natural course of disease, likely complications, prognosis, importance of a regular follow and the need of a prenatal evaluation in the event of a future pregnancy.

The infant was called for the first follow-up visit after a month, and thereafter every 1–2 months to check blood glucose records and review all aspects of Insulin dosing and administration. His growth parameters were recorded 3 monthly, ultrasound done 6 monthly, and skeletal survey done at first visit, and thereafter 6 monthly. Blood investigations such as HbA1c, blood counts, liver and kidney function tests and electrolytes were performed 3 monthly. Thyroid function test was done at first visit and then 4–6 monthly. The home monitoring of blood glucose was done regularly and readings were mostly within 80-190 mg/dl range. The kidney function tests, thyroid function tests and skeletal survey were normal. The child, however, displayed growth retardation [Figure 1] and delay in acquisitions of developmental milestones since early follow-up.

At the age of 2½ years, the thyroid function tests revealed central hypothyroidism (thyroid stimulating hormone

2.34 IU/ml, free thyroxine 0.51 ng/ml, free triiodothyronine 3.03 pg/ml) for which he was initiated on thyroxine 50 µg/day. Ultrasound of the neck showed a normally formed thyroid gland and thyroid scan showed normal uptake and size. Magnetic resonance imaging of the brain was done for pituitary evaluation and showed a normal size and position of the pituitary gland. To evaluate other pituitary hormones, serum adrenocorticotropin and cortisol were tested and were normal. The skeletal survey at 3 years showed small and poorly formed, irregular, and sclerotic epiphyses of the long bones along with flattened vertebral bodies suggestive of spondyloepiphyseal dysplasia [Figure 2]. He was also diagnosed to have iron deficiency anemia (Hb 8.9 g/dl, microcytic hypochromic anemia, serum ferritin 4 µg/L) and with iron supplementation it improved to Hb 11 g/dl.

By 4 years, the renal parameters got deranged along with persistent hyperkalemia, normal anion gap metabolic acidosis and estimated glomerular filtration rate of 50 ml/min/1.73 m² (chronic kidney disease [CKD] stage 3A). Ultrasonography revealed small size kidneys with raised echogenicity (right kidney 58 mm × 24 mm and left kidney 55 mm × 29 mm). The developmental assessment revealed a developmental quotient of 50% (motor 50%, social 67% and language 33%) and social quotient of 70%, thus making a diagnosis of global developmental delay (consistent with the underlying syndrome). Hearing, tested by pure tone audiometry, was within normal limits bilaterally. Vision was emetropic on dilated cycloplegic refraction and fundus was normal. A clinical timeline is presented in Figure 3.

At 6 years, his height is 86 cm (−5.96 Z as per Indian Academy of Pediatric chart) with upper segment to lower segment (US: LS) ratio of 1.1 which is attributed to skeletal dysplasia [Figure 4]. Currently, the child is receiving basal bolus regime (regular and glargine Insulin) with Insulin requirement 1.2 units/kg/day and last HbA1c 7.7% (June 2022). He is also receiving thyroxine supplementation (75 µg/day). For CKD, he requires potassium binder and oral bicarbonate on a daily basis and periodical injectable erythropoietin.

Over the follow-up years, the child has not developed any episode of DKA and is compliant with his treatment. Blood glucose is being monitored diligently at home including use of continuous glucose monitoring system for a few weeks. He has required 2 brief admissions for 2–4 days for monitoring and control of his blood glucose and has received one transfusion of packed red cells in his 4th year. Although hepatic dysfunction is a frequent association with WRS, it has still not emerged in this case. A younger sibling has been born and is now 3-years-old, alive and healthy. Prenatal diagnosis was done and did not reveal mutation.

Discussion

WRS is a rare autosomal recessive disorder, originally described in 1972 in siblings with early onset diabetes and skeletal dysplasia and most reported cases are from Middle East.[6,7] It is the most common cause of permanent neonatal diabetes in consanguineous pedigrees, accounting for 15 of 63 (23.8%) consanguineous probands of permanent neonatal diabetes.[4] It is caused by mutation in EIF2AK3 gene located at chromosome 2p12 that encodes for pancreatic endoplasmic reticulum kinase, a key enzyme for initiating cellular response to endoplasmic reticulum stress. The loss of function mutation leads to accumulation of misfolded proteins causing cell apoptosis. This gene is predominantly expressed in pancreatic beta cells and bone leading to universal

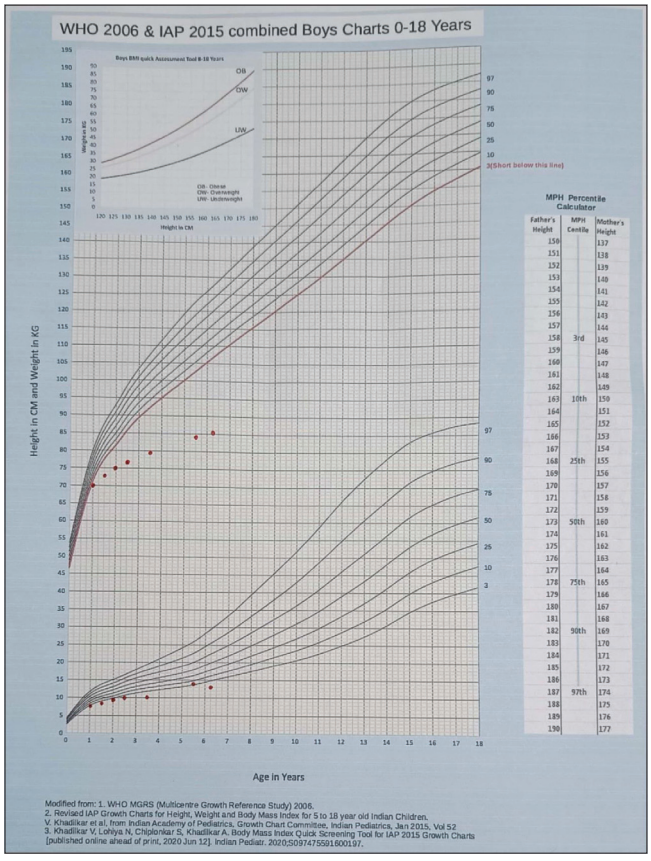

Figure 1: Growth chart of the child

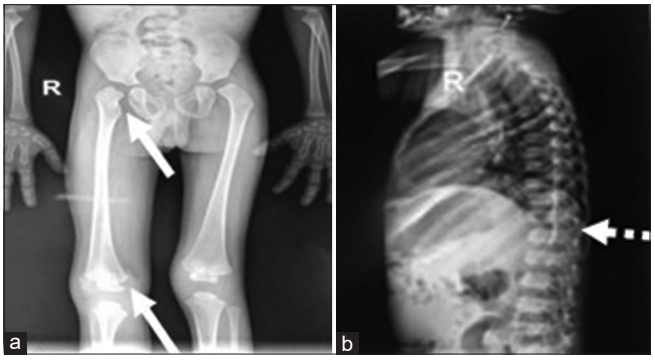

Figure 2: (a) Small, sclerotic epiphysis with irregular border at the head of femur and (b) flattened vertebral bodies suggestive of spondyloepiphyseal dysplasia

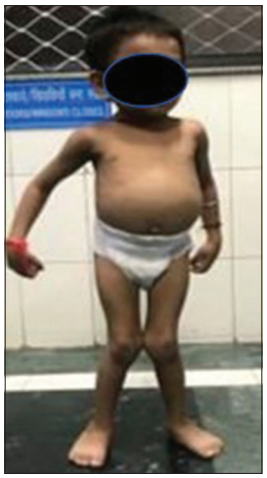

Figure 3: Index case with short stature and genu valgum deformity due to spondyloepiphyseal dysplasia

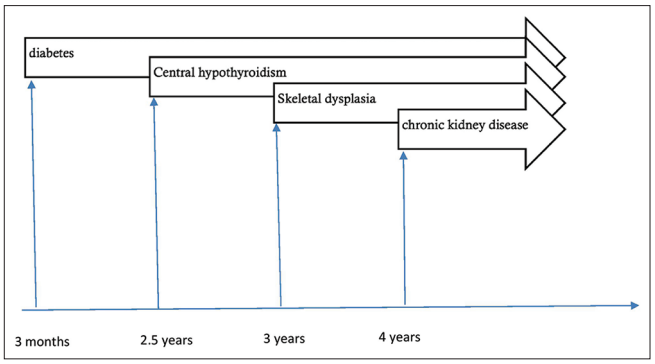

Figure 4: A timeline of various manifestations of WRS in the child. WRS: Wolcott Rallison syndrome

manifestation of diabetes mellitus and bony dysplasia in this syndrome.[8] Compound heterozygous variations of the gene have been recently reported to cause WRS in two children from nonconsanguineous parents.[9] Apart from early onset diabetes and skeletal dysplasia, other manifestations include hepatic dysfunction, renal dysfunction, exocrine pancreatic insufficiency, neutropenia, and developmental delay. Owing to the various associated features, the lifespan is short with a mean survival of 5.8 years, though a case from Kuwait was last reported alive at 17.5 years age.[7,10]

Diabetes mellitus typically presents within the first 6 months of life though some may be diagnosed later, even at 2 years of age.[7] It is a nonautoimmune Insulin requiring diabetes.

Skeletal dysplasia is the other cardinal finding and presents as small and irregular epiphyses, enlarged metaphyses, flattened acetabulum, and variable degrees of osteopenia.[11] There could be fractures and atlantoaxial dislocation. Short stature seen in WRS cases also is a result of skeletal dysplasia. Our case also had significant skeletal dysplasia and short stature.

Hepatic dysfunction is a frequent association and presents as intermittent hepatitis characterized by hepatomegaly, jaundice, and raised liver enzymes.[7] It was noted in 60% of 35 cases of Ozbek *et al*.[12] The hepatic histology could vary from mild lobular infiltration by lymphocytes to progressive fibrosis. Renal dysfunction, reported in 1/5th of cases by Ozbek *et al*.[12] could present as intermittent episodes of renal insufficiency or CKD which has manifested in this patient. Developmental delay and learning difficulties are present in the majority of cases.[11] Our case also had significant developmental delay. Neutropenia has been reported in a few cases and seems to be specifically associated with W522X mutation of the EIF2AK3 gene.[12]

Central hypothyroidism has been reported in 4 of 18 cases described by Senée *et al*.[11] Bin-Abbas et al. described two siblings with central hypothyroidism with normal imaging of hypothalamic pituitary region.[13] Our case was detected to have central hypothyroidism at 3 years of age without deficiency of other pituitary hormones and normal imaging. There have been occasional reports of primary hypothyroidism as well.[14,15] The short stature seen in this child despite being on thyroxine can be explained by the concurrent skeletal dysplasia and CKD.

Exocrine pancreatic insufficiency has been reported infrequently and may require pancreatic supplements.[12] However, our case has not developed clinical features of exocrine pancreatic insufficiency such as chronic diarrhea or oily stools.

WRS, due to mutations in EIF2AK3 gene, has a multitude of manifestations, with neonatal diabetes and skeletal dysplasia and variable presence of renal dysfunction, hepatic dysfunction, neutropenia, exocrine pancreatic deficiency, and delay in growth and development.

Our case presented as neonatal diabetes and evolved to manifest most of the features described above. The definitive diagnosis based on genetic analysis was established early on, at the first presentation itself. A detailed explanation of the condition to the parents also helped in ensuring a long and continuing follow-up in a disorder that otherwise has a dismal prognosis. One of the major factors behind the success of our management in an otherwise difficult disease is the extremely supportive and compliant family. regularity of follow up and adherence to our instructions has been crucial for the early identification of the various manifestations as they evolved and progressed. Let us hope that our case also has a long life like the one from Kuwait.

Lessons learnt

- Neonatal diabetes is a monogenic disorder and genetic analysis for detecting mutations should be carried out as early as possible
- WRS should be suspected in cases of neonatal diabetes in consanguineous pedigrees
- A regular follow-up for early detection of complications is crucial in the management of syndromic forms of permanent neonatal diabetes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal patient identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Wilke's Syndrome: A Missed Diagnosis in Pulmonary Tuberculosis in an Adolescent

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Abstract

Background: Superior mesenteric artery (SMA) syndrome or Wilke's syndrome is a rare, atypical cause of upper gastrointestinal tract obstruction. It occurs due to acute angulation between SMA and aorta causing compression of the third part of the duodenum inbetween them leading to proximal intestinal obstruction. **Clinical Description:** SMA syndrome occurs mostly in patients who have significant weight loss. It occurs mostly due to the loss of the retroperitoneal fat pad, which serves as a cushion for the duodenum protecting it from compression between the two arteries. Causes include prolonged supine bed rest, spine surgery, an unusual high insertion of ligament of Treitz, other causes leading to weight loss, and congenital anatomical defects. Symptoms include weight loss, bilious vomiting, pain abdomen, postprandial nausea, early satiety, and anorexia. We report a 14-year-old female, a known case of pulmonary tuberculosis, who developed pneumothorax followed by acute gastric dilatation superadded with septicemia and upper gastrointestinal tract obstructive symptoms during the hospital course. **Management:** Detailed history and radio imaging such as barium studies or contrast-enhanced computerized tomography abdomen are required for diagnosis. Treatment includes conservative management such as gastric decompression, maintenance of electrolytes, nutritional rehabilitation via nasojejunal feeding, orally or parenterally. Treatment aims to restore the mesenteric fat pad to increases the angle between the two arteries. If it fails, surgery needs to be planned wherein duodenojejunostomy can be performed. **Conclusion:** An increased index of suspicion should be kept for this rare syndrome in children, especially in cases associated with significant weight loss. This may lead to timely diagnosis and saving a precious life.

Keywords: Intestinal obstruction, superior mesenteric artery syndrome, weight loss

Superior mesenteric artery (SMA) syndrome, also known as Wilke's Syndrome, is an atypical cause of upper gastrointestinal tract obstruction. Acute angulation between the SMA and the aorta causes compression of the third part of the duodenum in between, leading to proximal intestinal obstruction. The incidence of SMA in the general population is 0.013%–0.3%,[1] and it is rare in children. Usually, retroperitoneal fat serves as a cushion for the duodenum along with the surrounding lymphatic tissue and protects it from compression by the two arteries.[2] Thus, Wilke's syndrome occurs mostly in situations when there is significant weight loss. Causes include prolonged supine bed rest, spinal surgery, an unusual high insertion of the ligament of Treitz, along with a congenital anatomical defect involving embryonic duodenal rotation and fixation.

The obstruction can be acute (complete/partial) or chronic. Symptoms vary accordingly and include weight loss, bilious vomiting, pain abdomen, postprandial nausea, early satiety, and anorexia.[3] The severity of symptoms is mainly affected by the degree of compression, depending on the angle between the SMA and the aorta (aortomesenteric angle). These include dehydration, electrolyte imbalance, malnutrition (wasting), perforation, and peritonitis. Treatment includes attempts to cause weight gain and restore mesenteric fat pad. This can be done either orally or parentally. If this strategy fails, surgery involving duodenojejunostomy needs to be planned.[4]

Pediatricians are generally unaware of this condition in children with significant weight loss. We lost one precious life due to delayed diagnosis. Albeit earlier case reports of SMA from India have been after spinal surgery, renal tubular acidosis and Marfan syndrome but none with underlying tuberculosis (TB). The aim of presenting this case is to increase the index of suspicion to increase early diagnosis and timely management.

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Clinical Description

A 14-year-old girl was brought to our emergency with complaints of productive, purulent, non-blood-tinged cough for 5 days. This was followed by acute onset of difficulty in breathing for 36 h before presentation, which progressively increased. It was associated with chest pain that was stabbing in nature and got aggravated with movement and cough. There was a significant past history of prolonged cough, fever, and weight loss 9 months back earlier, for which she had been investigated and diagnosed with pulmonary TB. This had been on the basis of chest X-ray and sputum for cartridge-based nucleic acid amplification test (CBNAAT). The patient had been started on anti-TB therapy (ATT). At the time of admission, she was in the continuation phase of ATT (rifampicin, isoniazid, and ethambutol) as per standard protocol (National Tuberculosis Elimination Programme 2020). Drug compliance was satisfactory. The child's respiratory symptoms had resolved, but her appetite was still poor even after the past 8 months. Her diet had a prolonged daily deficit of 35% and 25% calories and proteins, respectively. Besides this, there was no past history of any trauma, or prolonged bed rest/immobilization. No other member of her family had TB (negative sputum CBNAAT and X-ray chest). The child was immunized as per her age and had received the BCG vaccine. She studied in class 8, was an average student and belonged to the upper-lower socioeconomic status.

At the presentation, the patient looked anxious and was oriented to time, place, and person. Her heart rate was 115/min, respiratory rate 38/min, and she had oxygen saturation of 91% in room air. Nasal flaring was evident, with no obvious chest retractions. Her peripheries were cold and peripheral pulses feeble, though the central pulses were palpable. The blood pressure was 114/76 mm of Hg (between 50th and 90th centiles, Indian Academy of Pediatrics [IAP] growth chart). Her body mass index (BMI) was 13.9 kg/m^2 (<3rd centile for age, revised IAP growth chart of BMI for 5–18-year-old Indian children, 2015), indicative of severe thinness. There was no pallor, cyanosis, icterus, clubbing, or significant lymphadenopathy. The respiratory system examination revealed a shift of the trachea and apex beat to the left side, with decreased chest expansion on the right side. The percussion note was hyperresonant on the whole of the right side, more anteriorly than posteriorly, with decreased vocal fremitus. Liver dullness shifted downward. The air entry was markedly decreased on the right side with absent added sound (no wheeze, crepitations or whispering pectoriloquy) and absent vocal resonance. The abdomen was soft, nontender, and nondistended abdomen and there was no palpable organomegaly. The bowel sounds were present. The remaining systemic examination was normal. On the basis of history and examination, we kept a differential diagnosis of pulmonary TB (possibly drug resistant), complicated by a right-sided pneumothorax with septicemia and compensated shock. The patient was started on 100% oxygen with a partial rebreathing mask, and a normal saline intravenous (IV) bolus was administered (@10ml/kg). Investigations (routine blood tests, sepsis screen, chest X-ray, CBNAAT, and cultures) were planned accordingly.

Management and outcome

The patient's condition improved hemodynamically. A chest X-ray confirmed our clinical suspicion of right-sided pneumothorax, mediastinal shift to the left side, and multiple heterogeneous opacities bilaterally. An intercostal chest tube was inserted to resolve the pneumothorax. The hemogram showed hemoglobin of 11.2g/dl, white blood cell count of 13,900/mm^3 with neutrophilic predominance (62%), and platelet count of 175,000/µL. The C reactive protein was elevated (68.31 mg/L). Serum sodium levels were 131 meq/L, Potassium 4.3 meq/L. The total serum bilirubin was 0.4 mg%, SGOT/SGPT 71, and 45 IU/L, respectively. Her blood urea and serum creatinine levels were 31 mg% and 0.6 mg%, respectively.

Treatment comprised IV fluids, IV antibiotics (ceftriaxone @75 mg/kg/day q 12 h and injection ampicillin and cloxacillin @ 200mg/kg/day of ampicillin base every 6 h) were given for 10 days. ATT was continued. There was gradual symptomatic relief in terms of her respiratory symptoms along with the radiological resolution of the pneumothorax. The gastric aspirate CBNAAT showed the presence of *Mycobacterium tuberculosis* sensitive to rifampicin. Hence, the ATT was continued. Nasogastric feeding was started on the 3rd day of admission. The patient developed acute hepatic dysfunction on day 15 of hospitalization (SGOT/SGPT increased to 176 IU/L and 237 IU/L, respectively, and serum bilirubin was 1.4 mg%), which was presumed to be ATT induced, since viral serology markers for hepatitis B, hepatitis C, and human immunodeficiency virus were negative. ATT was modified as per standard protocol for 2 weeks.

On the 24th day of hospitalization, the patient developed mild respiratory distress again. There was X-ray showed multiple heterogeneous opacities with no sign of pneumothorax, so IV antibiotics (amoxycillin and potassium clavulanate @ 100mg/kg/day of amoxycillin base every 8 hours) were started. The patient displayed loss of weight as evident from the loosening of clothes and increasing visible wasting. On day 33 of admission, the patient developed mild abdominal distension, bilious vomiting, and non-passage of stools over 3 days. The LFTs and serum potassium were normal. An abdominal X-ray showed a large gastric shadow [Figure 1]. She was kept nil per oral, and nasogastric tube drainage was started with fluid replacement. The pediatric surgery team was consulted who advised to the continuation of conservative management and a contrast-enhanced computerized tomography (CECT) of the abdomen. Injection Meropenem (@ 60mg/kg/day every 8 h) was added, suspecting nosocomial infection. While awaiting the report, the patient developed an acute

episode of abdominal pain associated with a change in the nature of draining gastric aspirate from bilious to feculent, loss of consciousness (Glasgow Coma Scale total score 5 with E2V2M1), and peripheral circulatory failure. The patient was intubated, ventilated, and resuscitated as per standard protocol but could not be revived. The CECT report collected posthumously confirmed massive gastric dilatation [Figure 2] and also identified a decreased angle between the SMA and aorta, suggestive of SMA syndrome [Figure 3]. The family refused consent for performing an autopsy. The final diagnosis of pulmonary TB with severe thinness with SMA syndrome was made.

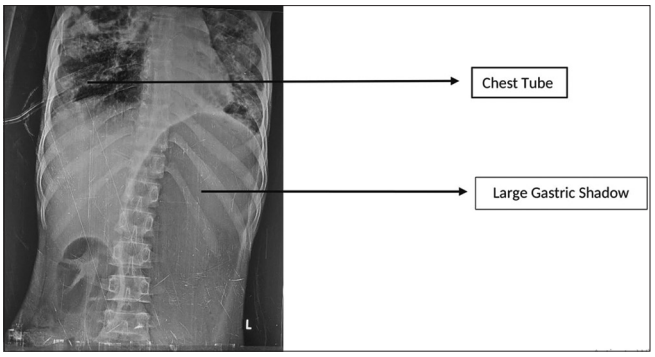

Figure 1: X-ray abdomen showing large gastric shadow

Discussion

The characteristic radiological features of SMA syndrome is the narrowing of the aorta-SMA angle to <20° (in this case, it was <17°), causing the aortomesenteric distance to decrease.[5] [Figure 3]. Here, the distance between the two arteries was <6 mm against the normal range of 8–12 mm.[6] Barium studies show dilatation of the first and second parts of the duodenum with the backflow of the barium proximal to obstruction, and which gets relieved in the prone or lateral positions.[4] Radio imaging-specific modalities such as CECT or magnetic resonance angiography (whichever is available) confirm the diagnosis. We performed the CECT abdomen due to the clinical condition of the patient, as the availability of the report is faster in our center.

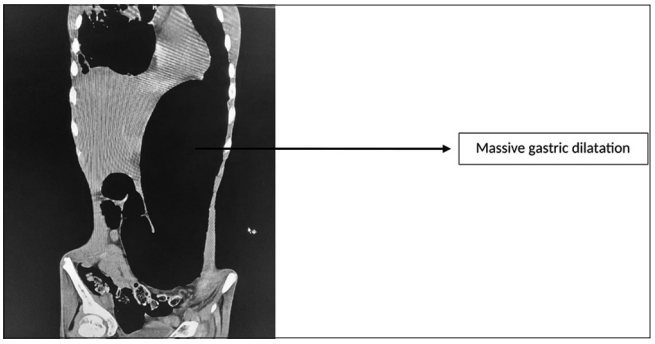

Figure 2: CECT abdomen (coronal view) showing massive gastric dilatation. CECT: Contrast-enhanced computerized tomography

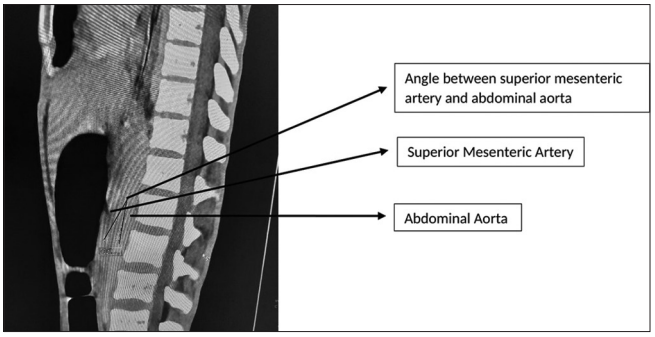

Figure 3: CECT abdomen (sagittal view) showing decreased angle between the superior mesenteric artery and aorta. CECT: Contrast-enhanced computerized tomography

Treatment of SMA syndrome includes conservative management like gastric decompression, maintenance of electrolyte balance, and nutritional rehabilitation, which can be done enterally via nasojejunal feeding (thus bypassing the obstruction) or parenterally, followed by oral feeds when the condition permits.[7-9] Positioning maneuvers like lying on the left side or assuming the knee-chest position can be tried during the feed. The ultimate goal is to increase the weight so that the pad of fat develops at the mesenteric root. If conservative management fails, surgery is considered.[4] This may be by duodenojejunostomy to relieve the obstruction. Gastro-jejunostomy was done previously, but there was a high incidence of complications like blind loop syndrome and recurrence. Strong's procedure, i.e., lysis of the ligament of Treitz with mobilization of the duodenum, can also be performed. However, this is associated with a failure rate of 25%.[5]

Acute massive gastric dilatation is a rare emergency that usually occurs in the setting of a closed-loop obstruction, rarely seen in chronic medical illnesses. It is usually managed conservatively, with only a few cases requiring surgical intervention. In our case, the patient was managed medically, suspecting acute gastric dilatation due to worsening sepsis since an electrolyte imbalance was ruled out.

SMA syndrome secondary to TB has been reported in a 59-year-old patient,[10] but there are no case reports in children or adolescents. Abdominal lymphadenopathy, mucosal edema, ulceration, bowel wall thickening, and scarring in the ileocecal region are usual in abdominal TB resulting in subacute or acute intestinal obstruction. These findings were not seen in our patient. In this patient, the risk factors for causing SMA syndrome were probably cachexia due to TB coupled with prolonged immobilization during her hospital stay. The prognosis depends upon how early the syndrome is suspected and diagnosed, with the mortality rate as high as one in three affected patients. Thus, an increased index of suspicion should be kept for this rare syndrome in children, especially in cases associated with significant weight loss. This may lead to timely diagnosis and saving a precious life.

Lessons learnt

- In any chronic debilitating condition, sudden gastric dilatation with features of intestinal obstruction should alert the treating physician to suspect Wilkie's syndrome
- It can be diagnosed by radio imaging like barium studies or CECT abdomen
- If aggressive conservative management fails duodenojejunostomy should be performed
- Appropriate nutritional rehabilitation in chronic hospitalized patient must be ensured to prevent this condition.

Declaration of patient consent

The authors certify that they have obtained the appropriate consent from the parent. The legal guardian has given his consent for the images and other clinical information to be reported in the journal. The guardian understands that the name and initials will not be published, and due efforts have been made to conceal the same, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Aggressive Systemic Mastocytosis with a Relatively Non-aggressive Course

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Abstract

Background: Mastocytosis is a heterogeneous group of disorders that is characterized by excessive proliferation and pathologic accumulation of mast cells in various body tissues. The mast cells also have abnormal morphology and aberrant expression of surface receptors. **Clinical Description:** A 4-year-old boy was brought with a history of generalized skin lesions since birth and abdominal distension for 3 years. The diagnosis had not been established to date. General physical examination revealed severe acute malnutrition, pallor, dental staining, facial hypertrichosis, polymorphous skin lesions (cicatricial alopecia, diffuse erythema, multiple plaques of variable diameter, skin-colored nodules, and hypertrophic irregular scars), and positive Darier's sign. He also had hepatosplenomegaly. The differentials considered were congenital erythropoietic porphyria, systemic mastocytosis (SM), multifocal Langerhans cell histiocytosis, and linear immunoglobulin A bullous dermatosis. The presence of mast cells on skin biopsy and elevated serum tryptase levels led us to suspect SM and perform bone marrow studies. The diagnosis of "aggressive" SM was initially made on the application of the diagnostic criteria but revised to "smoldering" SM with the emergence of Vitamin B12 deficiency as the probable cause of pancytopenia. **Management:** Management was planned by a multidisciplinary team: pediatrician, dermatologist, and hematopathologist. The parents were counseled about the nature, natural history, treatment options, and prognosis of the disorder. The child was provided with nutritional rehabilitation and medication for the cutaneous symptoms (selective histamine H1 receptor inverse agonist, H2-receptor antagonist, and application of topical tacrolimus and calamine lotion). **Conclusion:** The prognosis varies according to subtype. Careful correlation of clinical and laboratory investigations is required when applying the diagnostic criteria for staging.

Keywords: Darier's sign, KIT mutation, mast cells, serum tryptase, urticaria

Mastocytosis is a heterogeneous group of disorders that is characterized by excessive proliferation and pathologic accumulation of mast cells in various tissues of the body. The cells may also have abnormal morphology and aberrant expression of surface receptors.[1] The overall prevalence of mastocytosis is 1 in 10,000, out of which two-thirds are diagnosed in children.[1] The age of onset of symptoms is variable; 55% presenting from birth to 2 years, 10% up to 15 years, and 35% in individuals older than 15 years.[2] There is a slight male preponderance, with a sex ratio of 1.4:1.[3] Most cases are sporadic and 4% are familial.[3]

Mastocytosis is classified as cutaneous melanoma (CM) when manifestations are limited to the skin and systemic mastocytosis (SM) when there is additional involvement of other tissues/organs. SM is very rare, accounting for <10% of cases.[4] It is characterized by flushing, pruritus, abdominal pain, diarrhea, hypotension, syncope, and musculoskeletal pain. These features are due to mast cell mediator release (primarily histamine) and tissue/organ infiltration. The severity and prognosis are variable, depending on the subtype.

The etiology of SM is still unclear. It has frequently been associated with a functional mutation of the somatic proto-oncogene KIT gene (CD117) found on 4q12 and is therefore not hereditary. This locus encodes tyrosine kinase receptors that are expressed on mast cells and hematopoietic stem cells. Most affected adults display mutations of KIT codon D816V in exon 17, in contrast to only 42% of pediatric patients. In children, mutations have also been found in exons 8, 9, 11, and 13.[5] Mutations result in the loss of function of

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hematopoietic stem cell factor, leading to clonal proliferation and increased longevity of the mast cells.[1]

SM is often mistaken for the more common childhood dermatological disorders associated with pruritis, such as urticaria and eczema secondary to allergens, insect bites, bullous impetigo, rare autoimmune bullous disease, and linear immunoglobulin (Ig) A bullous dermatosis.[6] The purpose of sharing our experiences in managing this case is to increase awareness among clinicians and to highlight the challenges we faced in establishing subtypes.

Clinical Description

A 4-year-old boy presented with generalized skin lesions since birth. Historically, there were two types of lesions. The first was large blisters which ruptured discharging blood and healed with scarring. These had been noted on his back at birth. Since then, they had developed everywhere on his body, except his palms and soles. The parents had noted that fresh lesions appeared after minor trauma or scratching. The second lesions were multiple, itchy, raised, reddish-to-brownish, round-to-oval lesions, of varying size and generalized distribution. These got transiently relieved by medication, the nature of which was unknown. Neither lesion was associated with sneezing, wheezing, or watering, redness of the eyes, or increased exposure to sunlight or ingestion of drugs.

The child also had abdominal distension for 3 years, insidious in onset and gradually increasing. There was no history of abdominal pain, altered bowel habits, vomiting, jaundice, or decreased urine output. There was no significant antenatal, perinatal, or past history. The child was sixth in the birth order, of a nonconsanguineous marriage. Other family members were asymptomatic. He was developmentally normal, completely unimmunized, and belonged to an upper–lower socioeconomic background. He had been treated intermittently, but without symptomatic resolution, or establishment of diagnosis.

The patient was afebrile and hemodynamically stable. His weight was 9.4 kg (−4 z-score), height 77.2 cm (−6 z-score), and mid-upper arm circumference 10.5 cm indicating severe acute malnutrition (SAM). The general physical examination revealed some pallor, dental staining, facial hypertrichosis, significant generalized lymphadenopathy, and multiple polymorphous skin lesions. The abdomen was uniformly distended with visible dilated veins [Figure 1]. The liver was enlarged (8 cm below the costal margin with a span of 14 cm). The surface was smooth and consistently firm, and the margins were sharp. Firm splenomegaly was noted (11 cm below the costal margin). Shifting dullness was absent. The remaining systemic examination was normal. Since the clinical phenotype was a chronic illness with onset since birth, cutaneous manifestations, and hepatosplenomegaly, we consulted colleagues in the dermatology department.

Many different lesions were identified: well-circumscribed (3 cm × 3 cm) plaques with scarring over the occiput

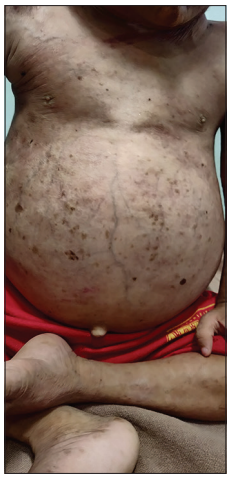

Figure 1: Distended abdomen with dilated veins, mild diffuse thickening of the skin, and postinflammatory hyperpigmentation

suggestive of cicatricial alopecia; faint diffuse erythema on his face, chest, and back; multiple dark-brown macules of variable size (0.5–1 cm in diameter) and diffuse thickening of the skin that resembled melanocytic nevi and mast cell infiltrates; multiple erythematous to skin-colored plaques of variable size (diameter 1–1.5 cm) over his face, neck, back, chest, and extremities [Figure 2]; a positive Darier's sign [Video 1]; multiple skin-colored nodules of variable size (1 cm × 1 cm–3 cm × 3 cm) over his axillae, back, and buttocks [Figure 2]; multiple hypertrophic irregular scars over the upper back suggestive of recurrent blistering [Figure 2], and that made us consider linear IgA bullous dermatosis.

The following differential diagnoses were considered: (i) congenital erythropoietic porphyria (CEP) – due to recurrent bullae, dental staining, and organomegaly, although reddish urine and photosensitivity were absent; (ii) SM – typical lesions observed with positive Darier's sign, hepatosplenomegaly, lymphadenopathy, and pallor, but gastrointestinal symptoms were absent; (iii) multifocal Langerhans cell histiocytosis – the presence of pallor, hepatosplenomegaly, generalized lymphadenopathy, and positive Darier's sign, but the absence of characteristic skin lesions, bony tenderness, or pulmonary, endocrinal, and gastrointestinal involvement; (iv) linear IgA bullous dermatosis – points in favor were the blisters, erosions, plaques, erythema, and hepatosplenomegaly (may be associated with lymphoproliferative disorders), whereas points against were the absence of "string of pearls" appearance, presence of nodules, and the fact that remission is seen in most children within 2 years of onset. Two differentials considered in view of generalized lymphadenopathy and hepatosplenomegaly but disregarded due to the polymorphic skin lesions, onset since birth, and indolent course, were acute lymphoblastic leukemia and hemophagocytic lymphohistiocytosis.

Management and outcome

The results of the preliminary investigations are given in Table 1. Salient findings were macrocytic anemia and bicytopenia, normal liver function test, renal function test, lipid

profile, and absence of eosinophilia. There was no evidence of sepsis (C-reactive protein 2.7 mg/dl, blood and urine cultures sterile). The absence of fluorescence on wood lamp examination and normal serum lactate dehydrogenase (253 IU/L) ruled out CEP. The skin biopsy taken from a nodule displayed positive special staining for mast cells indicative of CM. Given the presence of systemic features, we started investigating for SM. The serum tryptase level was increased (>200 µg/L). Fine-needle aspiration cytology of an inguinal lymph node showed polymorphous lymphocytes with numerous mast cells. Bone marrow aspirate showed an increase in mast cells in clusters, as well as scattered spindle forms. A few large atypical mast cells (round-to-oval with granular-to-hypogranular cytoplasm, central round-to-oval-to-spindle-shaped nuclei with coarse chromatin, and irregular nuclear membranes) were present. The erythroid series, myeloid series, and megakaryocytes were normal. Bone marrow biopsy revealed hypercellular marrow spaces (approximately 100%) with infiltration of the paratrabecular and intertrabecular regions by multifocal compact clusters of atypical mast cells [Figure 3a and b]. There were a few preserved areas of hematopoiesis. CD117 was positive on immunohistochemistry [Figure 3c].

The diagnosis of SM is established by the presence of one major and one minor, or three minor WHO diagnostic criteria. The major criterion is the presence of multifocal, dense infiltrates of mast cells (>15 in aggregates) in bone marrow (BM) or extracutaneous biopsies. The minor criteria include: (i) atypical morphology >25% mast cells on biopsy sections, (ii) KIT point mutation at codon 816 in the BM or another extracutaneous organ, (iii) CD2, and/or CD25 on mast cells, and (iv) serum total tryptase >20 ng/ml. Although mutation analysis or CD testing was not feasible due to financial constraints, one major and one minor criteria were satisfied.

Table 2 depicts the subtyping of SM based on various parameters: "B findings" or burden of disease, "C findings" or cytoreduction requirement, and mast cell leukemia (MCL). *Prima facie*, the subtype in this patient appeared to be

Table 1: Baseline investigation reports

Hemogram
Hemoglobin 8.17 g/dl, MCV 106.3 fL, MCH 32.4 pg, MCHC 30.5 g/dl
Reticulocyte count 4.83%
TLC 28,020/µL, absolute eosinophil count 130/µL
Differential leukocyte count: 66% neutrophils, 25% lymphocytes, 7% monocytes, 0.47% eosinophils, and 0.41% basophils
Platelet count 66,100/µL
Peripheral smear: Moderate anisocytosis, macrocytic and macroovalocytes RBCs, few polychromatophils seen. Platelets reduced. 35 NRBCs/100 WBCs seen
Kidney function test
Blood urea nitrogen 23.2 mg/dl, serum creatinine 0.25 mg/dl
Serum sodium 142 mmol/L, serum potassium 4.1 mmol/L
Serum calcium (total/ionized) 9.5 mg/dl/4.0 mg/dl, serum phosphate 3.87 mg/dl
Serum uric acid 5.5 mg/dl
Liver function test
Serum bilirubin (direct/indirect) 0.8 mg/dl/0.4 mg/dl
AST 11.8, ALT 8.5, ALP 198
Serum protein 7.09 g/dl, serum albumin 4.0 g/dl
PT 14.0 s (control 11.5 s), INR 1.22 s, aPTT 36.2 s (control 29.0 s)
Lipid profile
Total cholesterol 69 mg/dl
HDL 22 mg/dl, LDL 36.1 mg/dl, serum triglyceride 62.1 mg/dl
Ultrasound abdomen
Liver 9.5 cm, enlarged in size with normal echotexture. Spleen 12.5 cm enlarged in size with normal echotexture. Multiple enlarged, discrete, mesenteric, retroperitoneal, perisplenic, and periportal lymph nodes. The largest short-axis diameter is 2 cm. No evidence of necrosis. The right, and left kidneys are normal. No ascites

RBCs: Red blood cells, ALP: Alkaline phosphatase, ALT: Alanine transaminase, aPTT: Activated partial thromboplastin time, AST: Aspartate aminotransferase, HDL: High-density lipoprotein, INR: International normalized ratio, LDL: Low-density lipoprotein, MCH: Mean corpuscular hemoglobin, MCHC: MCH concentration, MCV: Mean corpuscular volume, NRBCs: Nucleated RBCs, PT: Prothrombin time, WBC: White blood cells, TLC: Total leukocyte count

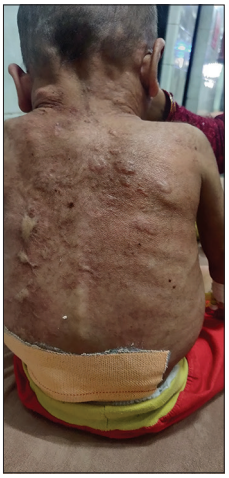

Figure 2: Polymorphic cutaneous lesions on the back showing diffuse, thickness of skin, erythematous to skin-colored plaques and nodules of variable size, scarring, postinflammatory hyperpigmentation, and melanocytic naevi

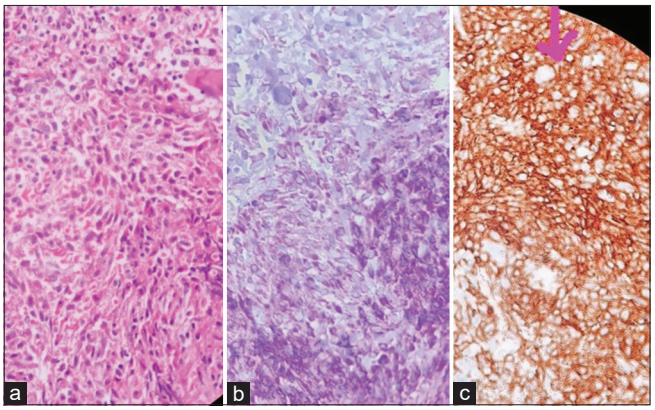

Figure 3: (a) Hematoxylin and eosin section of bone marrow aspirate showing increased mast cells in clusters, scattered spindle forms, and atypical and immature mast cells. (b) Special stain for mast cells (toluidine blue) positive. (c) Positive CD117 on immunohistochemistry

Table 2: Parameters required for subtyping of systemic mastocytosis

Burden of disease (B findings)	Cytoreduction requirement (C findings)	MCL
Bone marrow biopsy with >30% infiltration by mast cells (focal, dense aggregates) and/or serum tryptase >200 mg/ml	Bone marrow dysfunction manifested ≥1 cytopenia, but no obvious nonmast cell hematopoietic malignancy	Bone marrow biopsy shows diffuse atypical, immature mast cell infiltration
Signs of dysplasia or myeloproliferation in nonmast cell lineage(s) but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm with normal or slightly abnormal blood counts	Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension	Bone marrow aspirate with >20% mast cells
Hepatomegaly without impaired liver function, and/or splenomegaly without hypersplenism, and/or lymphadenopathy	Skeletal involvement with large osteolytic lesions and/or pathologic fractures	
	Palpable splenomegaly with hypersplenism	
	Malabsorption with weight loss due to gastrointestinal mast cell infiltrates	

MCL: Mast cell leukemia

aggressive SM (ASM) in view of 2 "C" findings, i.e., evidence of BM dysfunction (bicytopenia) and splenomegaly with hypersplenism (two cell lineages involved). However, a major point against it was the fact that survival beyond 2 years was not compatible with the natural history of ASM. The increased mean corpuscular volume and macrocytes prompted us to evaluate Vitamin B12 levels, which were low (109 pg/ml; normal 200–835 pg/ml), whereas folate levels were normal (6.07 nmol/ml). This was a more biologically plausible explanation for the cytopenias, especially since the typical BM findings of B12 deficiency could not be made due to the SM. Thus, on revisiting the criteria [Table 2], the presence of 2 "B" findings (>30% mast cells and hepatosplenomegaly in absence of dysfunction) satisfied "smoldering" SM, which was more in alignment with the clinical phenotype.

Management of SAM and the nutritional deficiencies proceeded as per hospital protocol. The parents were counseled about the nature, natural history, treatment options, and prognosis of SM. The cutaneous manifestations were treated with oral hydroxyzine (selective histamine H1 receptor inverse agonist), levocetirizine (H2-receptor antagonist), and the application of topical tacrolimus and calamine lotion. We could not consider midostaurin, an food and drug administration (FDA)-approved multikinase inhibitor effective in KIT D816V mutation.

Discussion

The diagnosis of SM in children is based on the 2016 WHO criteria which are completely investigation based.[7] Further delineation into subtypes based on severity is complex, basically determined by the additional presence of "B findings" indicative of infiltration without dysfunction, "C findings" indicative of infiltration with organ dysfunction, or MCL. There are seven subtypes: CM (no systemic involvement), indolent SM (ISM) (absence of B, C or MCL), smoldering SM (SSM) (≥2 B and no C), ASM (>1 C, no MCL), MCL +, SM associated with hematologic neoplasm (SM-AHN) (additional clonal hematologic nonmast cell lineage disorders), and mast cell sarcoma.[7,8] The prognosis depends on the subtype. Most studies of median survival of subtypes of SM have been done in adult patients.[9] Outcomes in terms of survival are relatively good in ISM and SSM, although 9.4% of cases of the latter progress to advanced SM.[10] ASM and SM-AHN are associated with poor prognosis, whereas MCL has the worst prognosis. We were unable to find similar studies in children, to help us prognosticate the parents.

Our case displayed some other atypical features. The presence of blisters since birth is exceptionally rare.[11] Bullous formation is due to histamine-induced capillary vasodilation and their presence in the neonatal period indicates a higher probability of having systemic involvement, poor prognosis, and early death.[12] This was not true in this case. At admission, the total leukocyte count was significantly elevated and mainly neutrophilic (in the absence of sepsis). The former can be explained by the release of proinflammatory and chemotactic factors by mast cells that affect leukocyte migration and recruitment, leading to leukocytosis. Our patient also had thrombocytopenia in contrast to the thrombocythemia that has been reported earlier with SM.[13] However, this could be explained by the Vitamin B12 deficiency, rather than BM dysfunction due to a "C" finding [Table 2].

The management of SM is multidisciplinary involving clinicians (the pediatrician and/or dermatologist depending on to whom the child presents) and hematopathologists. As there is currently no available cure, the goals of treatment are to mitigate organ damage, alleviate symptoms, improve the quality of life, and achieve long-term disease control.

Therapeutic options are according to the subtype. In ISM, the goal of treatment is to avoid the induction of mast cell release and control the resultant symptoms. The drugs used for symptomatic relief are H1 or H2-receptor blockers, mast cell membrane stabilizers (sodium tryptophan), leukotriene inhibitors (montelukast), and nonsteroidal anti-inflammatory drugs.[4] ASM should be treated with chemotherapy. Commonly used regimens include interferon-α alone or in combination with prednisone.[14] Tyrosine kinase inhibitors (TKIs), such as imatinib, dasatinib, midostaurin, hydroxyurea, and metaxalone may be used. Imatinib is suitable in SM due to KIT mutations that are sensitive to the drug, or those without KIT D816V mutations.[14] Midostaurin is the only TKI-approved monotherapy for ASM.[14] There is preliminary evidence that allogeneic hematopoietic stem cell transplantation (HSCT) may improve survival.[14] Since the role is still not definite, HSCT is generally reserved for patients who fail to respond adequately, relapse after initial therapy, or have adverse prognostic features.

It is important that the disease progression be monitored carefully in terms of the clinical and investigation profile. Patients are usually followed up every 1 to 3 months. This depends primarily on the burden of symptoms, overall clinical status, and whether any associated hematologic neoplasm coexists. In conclusion, due to its rarity, this condition may be easily missed unless clinicians keep a high index of suspicion and work in tandem with each other, as well as with hematopathologists.

Lessons learnt

- SM should be considered when chronic polymorphic cutaneous lesions and a positive Darier's sign are associated with the involvement of other organs
- The application of the WHO diagnostic criteria for the subtype of SM should be done with careful correlation with the clinical phenotype
- A multidisciplinary team comprising a pediatrician, dermatologist, and hematopathologist is required for diagnosis, staging, planning intervention, and monitoring.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Plasmodium vivax Malaria Associated with Severe Autoimmune Hemolytic Anemia

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Abstract

Background: Severe and/or persistent anemia due to autoimmune hemolytic anemia (AIHA) secondary to vivax malaria is a rare association. Very few cases are reported worldwide, and even less from India. AIHA occurs when immunoglobulins and/or complements target red blood cell surface antigens resulting in hemolysis. Awareness of this complication helps in early recognition, investigation, and prompt initiation of treatment. **Clinical Description:** A 15-year-old boy presented with a history of high fever associated with chills for 2 days. Examination revealed the presence of severe pallor and icterus. Systemic examination was unremarkable. Investigations showed anemia (Hb: 3.6 g/dl) with reticulocytosis (6.6%), malaria (trophozoites of *Plasmodium vivax* and antigen test positive), and indirect evidence of hemolysis (indirect hyperbilirubinemia and elevated lactate dehydrogenase of 668 U/l). **Management and Outcome:** Treatment was started with intravenous artesunate and packed cells transfusion was planned. Cross-matching showed autoantibodies which raised suspicion of AIHA. Coomb's test was positive. Least incompatible packed red blood cells were transfused. A repeat peripheral smear was negative for malaria. Posttransfusion, the Hb levels rose to 8.3 g/dl before falling to 5.3 g/dl over the next 2 days. The direct antiglobulin test was positive. High doses of oral prednisolone resulted in progressive improvement in Hb levels to 8 g/dl within a week. He was discharged on oral prednisolone with daily oral folic acid supplements. The steroids were tapered when Hb reached 10.6 g/dl and continued for 3 months. **Conclusion:** If a patient with malaria (falciparum or vivax) exhibits persistent severe anemia, indirect evidence of hemolysis is found on investigations and/or autoantibodies identified on cross-matching, AIHA should be suspected and investigated accordingly.

Keywords: Autoantibodies, autoimmune hemolytic anemia, malaria

Anemia is a known complication of malaria, more frequently due to *P. falciparum* than with *Plasmodium vivax* or other species of *Plasmodium*. Its rate of occurrence depends on the regional endemicity of malaria transmission and the age group affected.[1] The underlying causes of anemia in malaria are multiple: due to the invasion and destruction of red blood cells (RBCs) by the malarial parasite, splenic sequestration, ineffective erythropoiesis, and rarely, autoimmune hemolytic anemia (AIHA).

AIHA is characterized by RBC surface antigens being targeted by immunoglobulins and/or complements. An inappropriate immune response to an RBC antigen or to another antigenic epitope that is similar to an RBC antigen, known as molecular mimicry, may result in the production of the autoantibody. The RBC membrane may also be altered by an infectious agent that renders it "foreign" or antigenic to the host. These may be detected by getting a positive result on a direct Coomb's test (DCT).[2]

Globally, the annual incidence of AIHA in children is reported to be 1–3 cases per 100,000 patients.[2] Besides the fact that it is rare in malaria, the low numbers may also be due to the low index of suspicion of clinicians (and thus failure to look for supportive evidence), as well as underreporting of the cases that are diagnosed. Very few cases have been reported from India [Table 1].

Severe anemia is a complication associated with *Plasmodium falciparum* which is not usually found in *P. vivax*. Therefore, a thorough examination and proper investigations are necessary not only to find the etiology of severe anemia but also to prevent further complications. We present this case to highlight the association of AIHA with *P. vivax* and sensitize clinicians to consider this entity in malaria complicated with anemia, since its prompt diagnosis and management results in favorable outcomes.

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Clinical Description

A 15-year-old boy from a tribal area presented with high-grade fever associated with chills for 2 days, and yellowish discoloration of eyes for the same duration. There was a history of two episodes of nonprojectile and nonbilious vomiting. There was no history of dark/high-colored urine, gastrointestinal bleeding, or passing worms in stools. A history of pedal or facial swelling, oliguria/anuria, cough, chest pain, breathlessness, headache, or seizures was not elicited. He had not received any blood transfusion in the immediate past. He was diagnosed with *P. vivax* malaria on the basis of a positive lactate dehydrogenase (LDH) antigen test during a routine work-up for fever at another center and had been prescribed oral doxycycline, primaquine, and paracetamol. The child was brought to our hospital when the fever persisted and he developed severe prostration and severe pallor despite this treatment. There was no family history of any other cases of malaria or of bleeding tendencies and blood transfusions. His immunization status was appropriate for his age.

On examination, the child was sick and displayed severe prostration. He was severely pale and icteric. There was no cyanosis, petechiae, ecchymoses, pedal edema, lymphadenopathy, or dysmorphic features. He was febrile (axillary temperature: 102°F) with a pulse rate of 110 beats per min (regular, normovolemic, and all peripheral pulses palpable), respiratory rate of 24 per min, blood pressure 100/70 mmHg, and saturation of 97% in room air. His weight was 40 kg, height was 142 cm, and body mass index was 19.9 kg/m^2 (normal for his age). Salient systemic examination findings were normal vesicular breath sounds (no respiratory involvement), a hemic murmur at the apex of the heart (not in congestive heart failure), and the absence of hepatosplenomegaly.

Since the clinical history and investigations were suggestive, the primary diagnosis was severe anemia and jaundice due to complicated vivax malaria. However, hemolytic anemia due to G6PD deficiency was also considered he was from a tribal area and had received primaquine. Therefore, baseline investigations were ordered at admission to explore these possibilities and also rule out other organ dysfunction and septicemia.

Management and outcome

The hemogram showed hemoglobin (Hb) – 3.6 g/dl, total leukocyte counts – 7530/uL, platelets of 4.61 lakh/ul, with the peripheral blood smear showing trophozoites of *P. vivax*, normocytic normochromic red blood cells, occasional anisocytosis, and teardrop cells. The corrected reticulocyte count was 6.6%. The antigen test was positive for *P. vivax* and negative for *P. falciparum*. The liver function test demonstrated indirect hyperbilirubinemia without transaminitis (total bilirubin was 5.41 mg/dl, direct bilirubin – 0.82 mg/dl, indirect bilirubin – 4.59 mg/dl, serum alkaline phosphatase – 142 U/L, serum glutamic-oxaloacetic transaminase (SGOT) – 31 U/L, and serum glutamic-pyruvic transaminase (SGPT) – 10 U/L. An elevated LDH (668 U/l, normal 105–333U/l) indicated the possibility of hemolysis**.** The renal function tests were normal (blood urea: 30 mg/dl and creatinine: 0.77 mg/dl). Sepsis was ruled out as the C-reactive protein was negative**,** and cultures (blood and urine) were sterile. The PCR for the SARS-Cov-2 virus was also negative.

Treatment with isotonic intravenous (IV) fluids, IV artesunate (2.4mg/kg/dose) was started and 2 units of packed cells transfusion was planned. However, during cross-matching, autoantibodies were identified, raising suspicion of AIHA. This was supported by a positive DCT. Direct antiglobulin test (DAT) could not be done at this point of time to categorize the subclass. In these circumstances, the child was transfused with 2 aliquots of best-matched (least incompatible) packed red cells. The posttransfusion period was uneventful, and the Hb increased to 8.3 g/dl.

The fever persisted till the 5th day of admission even though there was no evidence of parasitemia on the peripheral smear. The Hb further dropped to 6.5 g/dl favoring the possibility of ongoing autoimmune hemolysis. Therefore, he was started on tablet prednisolone (40 mg/day orally in two divided doses) on the 6th day of admission. Although the fever subsided within 24 h, the Hb continued to decrease further requiring another transfusion of the least incompatible packed red blood cells. The dose of oral prednisolone was increased to 80 mg/day. Subsequent serial daily Hb estimations showed a gradual rise and the total bilirubin decreased to 2.06 mg/dl [Table 2]. Getting the DAT done became feasible and it was positive. The patient was discharged after 8 days with a Hb of 8 g/dl, with the advice to continue prednisolone for 3 months, along with oral folic acid supplementation (5 mg once daily).

Upon follow-up (7 days after discharge), the Hb had increased to 10.6 g/dl and we started tapering prednisolone by

Table 1: Case reports of post malaria autoimmune hemolytic anemia from India

Author	Patient details	Presentation	Hb (g/dl)	PS for malaria	DAT
Sonani *et al*.[2]	20-year-old male	Fever with chills - 7 days Yellow sclera and urine	3.2	*P. vivax* and *P. falciparum* positive	Positive
Singh *et al*.[3]	35-year-old female	Fever with chills - 7 days Jaundice 4 days	4.5	*P. vivax* positive	Positive
Ghosh *et al*.[4]	42-day-old male	Fever for 5 days and Jaundice	3.6	*P. vivax* positive	Positive
Taneja and Agarwal[5]	6-month-old male	Mild icterus, liver and spleen were enlarged	2.8	*P. vivax* positive	Negative
Sharma *et al*.[6]	Case series of 3 patients	High-grade fever with chills -yellow sclera and urine		*P. vivax* and *P. falciparum* positive	Positive

P. vivax: Plasmodium vivax, P. falciparum: Plasmodium falciparum, Hb: Hemoglobin, PS: Peripheral smear, DAT: Direct agglutination test

Table 2: Laboratory parameters of the child during hospital stay

Day	Hb (g/dl)	TLC (cells/m^3)	Platelets (lakhs/mm^3)	LFT	DAT	Additional information
1	3.6	7530	4.61	Total/direct/indirect bilirubin (mg/dl): 5.41/2.06/3.35 SGPT - 10 IU/L SGOT - 31 IU/L	Not done	Corrected reticulocyte - 1.7
2	6.1	-	-	-	-	Received 1 U PRBC
3	8.3	4720	3.64	-	Positive	-
5	6.5	4910	3.71	-	-	Oral prednisolone 40 mg/day
6	5.6	4270	4.58	-	-	Received 2 U PRBC Prednisolone 80 mg/day
8	8.0	6140	6.12	Total/direct/indirect bilirubin (mg/dl): 2.06/0.5/2.1 SGPT - 88 IU/L SGOT - 36IU/L	Positive	Corrected reticulocyte count - 5.4
14	10.6	-	-	-	-	Prednisolone tapered by 5 mg/week

Hb: Hemoglobin, TLC: Total leukocyte count, LFT: Liver function test, DAT: Direct agglutination test, PRBC: Packed red blood cells, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase

5 mg/week. A repeat DAT done 2 months after the hemolytic crisis was still positive with Hb 10.8 g/dl. A G6PD quantitative enzyme assay by the kinetic method was done just to rule out the possibility of G6PD deficiency. It was 8.59 U/g within the normal range. Thus, the positive malarial smear, severe anemia, reticulocytosis, positive DAT coupled with clinical and hematological improvement after corticosteroid therapy, and the absence of G6PD deficiency established the diagnosis of AIHA secondary to vivax malaria.

Discussion

Complicated malaria may present with prostration and multiple system involvement: neurological (impaired consciousness seizures), pulmonary (respiratory distress pulmonary edema), jaundice (as a consequence of hepatic dysfunction or hemolysis), hematological (hemoglobinuria, abnormal bleeding, and severe anemia), renal (acute kidney failure), and circulatory (shock).

Anemia in vivax malaria is caused by hemolysis, increased splenic clearance, and a variable degree of bone marrow ineffective erythropoiesis.[7] Vivax, malaria-induced AIHA, is an infrequent condition.[8] It varies in severity in childhood and is self-limited. Immune hemolytic anemia is mediated by antibodies directed against the erythrocyte surface antigens. The demonstration of antibodies to red blood cells (RBCs) by a positive Coombs test is essential.[3] Till date, only a few cases of AIHA in malaria patients are reported worldwide [Table 1]. The exact mechanism of AIHA in vivax malaria is not well understood but, nevertheless, AIHA should be considered and hemolysis looked for in vivax malaria if anemia persists (as in this case).

Typical laboratory findings of malaria include anemia, thrombocytopenia, and a normal or low leukocyte count with a positive smear or malarial antigen test. The erythrocyte sedimentation rate is often elevated.[9] The cause of indirect hyperbilirubinemia and elevated LDH was probably due to the ongoing intravascular hemolysis that was occurring due to the autoimmune antibody-mediated lysis of RBCs. This was evident by the positive DAT test that demonstrates the presence of antibodies or complement on the surface of red blood cells, the hallmark of autoimmune hemolysis.[10] Agglutination of erythrocytes with anti-IgG serum reflects warm AIHA, while a positive anti-C3 DAT occurs in cold AIHA.[11] In this case, subclass testing could not be performed. Direct antiglobulin/Coombs test results may remain positive even after Hb levels normalize.[12]

The disease tends to remit spontaneously within a few weeks or months. A consistent response to glucocorticoid therapy, low mortality rate, and full recovery are characteristics of the acute form of AIHA as seen in this case. Glucocorticoids decrease the rate of hemolysis by blocking macrophage function by downregulating Fcγ receptor expression, decreasing autoantibody production, and enhancing the elution of antibodies from the RBCs. Prednisone or its equivalent is administered at a dose of 2 mg/kg/day that may be increased to 6 mg/kg/day in severe cases to reduce the rate of hemolysis. In severe anemia, transfusions may be lifesaving, but it is critical to check for underlying alloantibodies that can hasten the hemolysis of transfused red blood cells.

Very few cases of AIHA in malaria have been reported from India [Table 1]. Ghosh *et al*.[4] described a 1-month-old infant who had a similar clinical presentation of high fever with pallor and jaundice but splenomegaly was present. Taneja *et al*.[5] reported a 6-month-old infant with fever, pallor, and jaundice with a positive smear for *P. vivax*. He received antimalarial treatment but later presented with severe anemia and hepatosplenomegaly with the clearing of malarial parasitemia. The serum of the recipient was incompatible with all the blood samples of the same group, but DAT was negative. A diagnosis of AIHA was made when he

demonstrated a clinical and hematological response to therapy with oral prednisolone. Splenomegaly is not always found in AIHA, as is evident in our case. Hence, AIHA should be suspected even in the absence of splenomegaly. To conclude, if a patient with malaria (falciparum or vivax) exhibits persistent severe anemia, indirect evidence of hemolysis is found on investigations and/or autoantibodies identified on cross-matching, AIHA should be suspected and investigated accordingly.

Lessons learnt

- Autoimmune mediated hemolysis, although a rare cause of anemia in vivax malaria should be considered when anemia persists
- Splenomegaly is not always detected in autoimmune hemolytic anemia. Hence, AIHA should be suspected even in absence of splenomegaly
- Prompt diagnosis of AIHA in malaria and early initiation of corticosteroids (which may require increase in dose) shows good clinical outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Cutaneous Tuberculosis: A Diagnosis Too Common, Yet Too Far

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Abstract

Background: Cutaneous tuberculosis (TB) is a rare disease seen by the pediatrician on an outpatient basis. It has a varied presentation and is classified on the basis of the source of infection and host's immune response to mycobacteria. Lupus vulgaris (LV) is a paucibacillary manifestation of cutaneous TB. It can mimic other infectious skin diseases such as TB verrucosa cutis and chromoblastomycosis. **Clinical Description:** We hereby present a case report of an adolescent female with a serpiginous, nodular, and warty hyperpigmented skin lesion over her buttock. The lesion had started following incidental injury 7 years back as a papule and continued to expand despite multiple medications. **Management:** A skin biopsy was done which was suggestive of cutaneous TB, but the absence of systemic features confounded the diagnostic type. She was finally diagnosed as having LV after a detailed review with a dermatologist and pathologist. The patient responded well to antitubercular treatment. **Conclusion:** Although cutaneous tuberculosis is well described, it is often not recognized by the primary care physician. Diagnostic dilemmas may arise due to clinical-histopathological mismatch.

Keywords: Histopathology, lupus vulgaris, tuberculosis verrucosa cutis

Tuberculosis (TB) in children remains a major health problem worldwide, especially in developing countries. Cutaneous tuberculosis (TB) is rare. It accounts for 1.5% of all cases of extrapulmonary TB.[1] It has varied clinical presentations ranging from papules, nodules, ulcers, and papillomatous lesions depending on the route of entry of the bacilli and immune status of the host. The two most common forms of childhood cutaneous TB are lupus vulgaris (LV) and scrofuloderma. LV is a paucibacillary manifestation of cutaneous TB. It is characterized by nodular, sharply defined, gelatinous lesions with centralized atrophy. Although the clinical presentation is quite suggestive of the diagnosis, it often gets delayed due to poor recognition by the treating physician or pediatrician. In India, the reported prevalence of childhood skin TB varies from 18% to 54%.[2] We report a case that was a diagnostic dilemma due to confounding clinical and histopathological interpretation.

Clinical Description

A 16-year-old girl came to the outpatient department with a skin lesion over her right buttock. It had appeared 7 years back following an incidental trauma with minimal bleeding. Thereafter, the lesion became dry, underwent scarring, and gradually expanded circumferentially. At presentation, there was no pus discharge, pain or itching locally. The surrounding skin was normal. The patient reported to have been seen by different physicians, advised multiple topical medications; the nature of which was not known, but the lesion continued to expand. There was no history of fever, cough, weight loss, anorexia, or contact with an active TB case. There was no history of any other skin lesion or similar lesion in any family member.

The patient weighed 55 kg and her height was 150 cm. Her body mass index was 24.4 Kg/m^2 normal for her age. Her heart rate was 88/min, respiratory rate 14/min, blood pressure 110/76 mm Hg and temperature 98.6F. There was no pallor or lymphadenopathy. On local examination, a nodular, warty, and hyperpigmented skin lesion was visible over the right buttock with serpiginous margins, measuring 8 cm × 14 cm. The temperature was not raised and there was no surrounding erythema. On systemic examination, respiratory examination revealed normal vesicular breath sounds, and no organomegaly was appreciated per abdomen. Other systems were normal.

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Management and Outcome

The history of trauma implicated the possibility of exogenous contamination. However, the absence of fever and prolonged duration without complications did not favour a chronic infection. An autoimmune or allergic etiology seemed unlikely in the absence of history of disease flare-ups. On review of literature and images in an atlas, we suspected LV, TB verrucosa cutis (TVC), and chromoblastomycosis. Their clinicopathological comparison is presented in Table 1.

A detailed evaluation was planned. Mantoux tuberculin skin test was positive (induration 32X28mm). Her abdominal sonogram and chest radiograph did not show any evidence of TB. A skin biopsy was performed. Figure 1 shows the presence of many intraepidermal lymphocytes, and the dermis showed lymphocytes, plasma cells, and occasional histiocytes. Well-formed granulomas were seen in the lower dermis. Ziehl–Nielsen stain for acid-fast bacilli (AFB) was negative. Mycobacterium was not detected on cartridge-based nucleic acid amplification. Periodic acid–Schiff stain was also negative. This stain helps to demonstrate glycogen, cellulose, mucin, starch, and certain fungi such as *Cryptococcus neoformans, Histoplasma capsulatum, Aspergillus fumigatus,* and *Blastomyces* because of the high carbohydrate content in their cell wall/capsule. No fungal element was seen on the KOH mount and no fungal growth was observed after 5 weeks of incubation on Sabouraud agar, thereby ruling out chromoblastomycosis.[3]

Although the histopathology report was suggestive of cutaneous TB, a diagnostic dilemma arose. Granulomas in the lower dermis pointed toward TVC, and this was also supported by the trauma. However, the dermatologists opinion based on clinical appearance was LV, though systemic manifestations of TB were absent. Since literature, reports clinicohistological concordance in 64%–85.6% cases of childhood cutaneous TB,[4] it was decided to start antituberculous treatment (ATT). There was a significant response with reduction in size within a month and complete resolution by 4 months [Figure 2].

Discussion

The clinicopathological manifestations of cutaneous TB are diverse. The precise diagnosis is often overlooked, due to confusing clinical presentations and no definitive diagnostic tool. The differential diagnosis includes sarcoidosis, leprosy, atypical mycobacterial infection, blastomycosis, chromoblastomycosis, actinomycosis, leishmaniasis, hypertrophic lichen planus, psoriasis, lupus erythematous, lymphocytoma, and Bowen's disease. The available investigative tools include Mantoux skin testing, chest X-ray, skin biopsy with histological analysis and special staining methods for identification of AFB, and cartridge-based nucleic acid amplification test; however, they have low sensitivity and specificity.

Cutaneous TB can be classified on the basis of the route of infection and pathogenic load. Multibacillary forms are detected in cutaneous tissue such as tuberculous chancre,

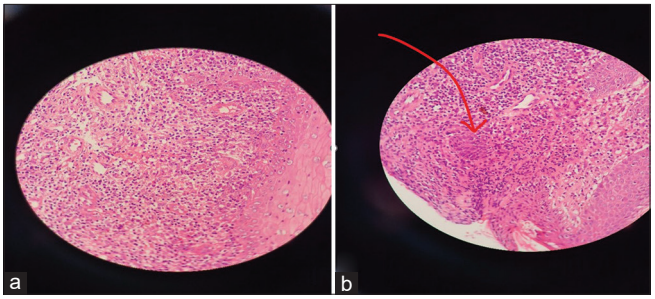

Figure 1: (a) Epidermis with granulation tissue in upper dermis, (b) Granuloma in lower dermis

Table 1: Differential diagnosis and pathological comparison

Name of disease	TVC	LV	Scrofuloderma	Chromoblastomycosis
Bacillary load of mycobacteria TB	Paucibacillary form	Paucibacillary form	Multibacillary form	Not applicable, fungal skin infection
Clinical picture	TVC starts as a single papule or nodule that slowly grows serpiginously as a warty hyperkeratotic plaque occurring at the site of trauma in individuals with strong immunity It occurs without any systemic manifestations or lymphadenopathy	Arises as an asymptomatic papule which progresses gradually to form a well-demarcated dry plaque LV presents with regional lymphadenopathy	It is characterized by asymptomatic subcutaneous swellings which persist for several months before softening and ulcerating to form discharging sinuses	Chromoblastomycosis presents as multiple nodular, verrucous, cicatricial, and tumoral forms
Histopathology	Dermal granulomas and pseudoepitheliomatous hyperplasia is seen	Upper dermal/epidermal granulomas are seen without caseation	Intense caseation is seen	Hyperkeratosis, parakeratosis, elongation of rete ridges, Medland or muriform bodies
Etiology	Direct inoculation of bacilli into the skin leads to infection	Infection is secondary to a preexisting primary focus spreading through lymphatic or hematogeneous dissemination	It arises due to contiguous spread of an underlying tuberculous focus to the overlying skin	Exogenous infection following trauma

TB: Tuberculosis, TVC: TB verrucosa cutis, LV: Lupus vulgaris

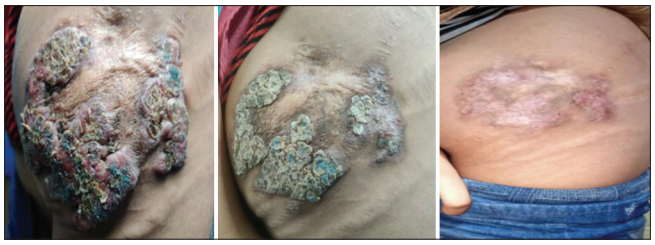

Figure 2: Warty lesion on the buttock, at 1 month following ATT, at 4 months of ATT. ATT: Antituberculous treatment

scrofuloderma, orificial TB, acute miliary TB, and tuberculous gumma. Paucibacillary forms include TVC and LV. Direct inoculation of bacilli into the skin leads to chancre or TVC.[5] Endogenous infection is secondary to a preexisting primary focus spreading contiguously (orificial TB and scrofuloderma), hematogeneously (acute miliary TB and tuberculous gumma), or through lymphatic dissemination (LV).[1] On histopathology, intense caseation is seen in scrofuloderma, dermal granulomas, and pseudoepitheliomatous hyperplasia in TVC and upper dermal/epidermal granulomas without caseation in LV.[6] According to a study conducted in an adult population from North India, the distribution of types of cutaneous TB was LV (55%), scrofuloderma (25%), orificial TB (5%), and TVC (5%).[7] The most common sites involved were hands, feet, or buttocks.[5]

Cutaneous TB may be an isolated finding as seen in our case or it may occur as disseminated TB in children. Case reports have described combinations of skeletal, ocular, and skin involvement making the diagnosis difficult.[8] TB of the central nervous system, knee joint, and skin has also been reported in which diagnosis was mistaken for connective tissue disease.[9] A common misdiagnosis is pyogenic abscess. The failure of therapeutic response to broad-spectrum antibiotics and isolation of mycobacteria establishes final diagnosis.[10]

TVC starts as a single papule or nodule that slowly grows serpiginously as a warty hyperkeratotic plaque occurring at the site of trauma in individuals with strong immunity.[4] It occurs without any systemic manifestations or lymphadenopathy. In comparison, LV is a chronic, progressive form that develops due to direct extension from underlying joints or lymph nodes through lymphatic or hematogeneous spread. LV presents with regional lymphadenopathy.

In conclusion, the diagnosis of LV can be considered in chronic painless skin lesions occurring as a direct extension of a TB focus, with strong Mantoux positivity, suggestive histopathological picture, and prompt response to ATT, especially in communities with high burden of cases of TB.

Lessons learnt

- Cutaneous TB is one of the differential diagnosis of chronic painless skin diseases.
- Systemic involvement may not be seen, but should always be evaluated to rule out dissemination of TB.
- Diagnosis of cutaneous TB is based on characteristic clinical morphology of the lesions. Laboratory tests may provide supportive evidence.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given consent for images and other clinical information to be reported in the journal. The guardian understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Lymphatic Malformation Presenting as Recurrent Pleural Effusion and Ascites

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Abstract

Background: Chylothorax is defined as the accumulation of chyle in the pleural space and is characterized by elevated triglyceride content in pleural fluid >110 mg/dl. Chylous ascites is the accumulation of chyle in peritoneal fluid characterized by triglyceride levels >200 mg/dL. Causes can be traumatic or nontraumatic; portal or nonportal; and congenital or acquired (inflammatory, postoperative, malignant, or infectious). Lymph duct abnormalities are a rare cause of concurrent occurrence of chylothorax with chylous ascites. **Clinical Description:** We report a 4½-year-old girl who initially presented a fever and was diagnosed to have right-sided pleural effusion. Since no other focus was identified, she was treated as a case of tubercular pleural effusion, following which her symptoms settled transiently. She thereafter had a recurrence of her symptoms in association with ascites and was managed as a case of relapse of tuberculosis (TB) with category 2 anti-tubercular therapy. Since her symptoms did not resolve, she was referred to our hospital for further management. **Management:** Clinical reasoning based on history and examination coupled with investigations ruled out cardiac, renal, hepatic, malabsorption, or nutritional pathologies of recurrent effusions. TB was ruled out. A lymphatic malformation was suspected. Therapeutic cum diagnostic paracentesis was done in a fed state, which indicated a chylous nature by the milky appearance and suggestive cytology and biochemistry. Lymphoscintigraphy confirmed the presence of a lymphatic duct abnormality. The child was managed with diet modifications, following which she improved within a week. **Conclusions:** The approach to recurrent effusions without any focus should be logical and sequential, as described above, to exclude the aforementioned common conditions. If workup for TB is repeatedly negative other less likely causes should be considered.

Keywords: Chylothorax, chylous ascites, lymphangiectasia

The concurrent occurrence of chylous ascites (CA) with chylothorax is rare in children, as well as the general population.[1] A tertiary care center reported an incidence of 1 in 20,000 admissions, inclusive of adults and children over a period of 20 years.[2] Congenital CA is associated with Klippel-Trenaunay and Yellow-Nail syndrome. The secondary causes of CA are heterogeneous and include lymphatic duct obstruction, chyle leakage through a lymphoperitoneal fistula, malignancy, postoperative complications, radiation, infections (i.e., tuberculosis (TB), filariasis), pancreatitis, sarcoidosis, pericarditis, blunt injury to the abdomen, hepatic cirrhosis, drugs (calcium channel blockers, sirolimus), portal vein thrombosis, and nephrotic syndrome.[3]

Loss of chyle results in significant loss of protein and fat with resultant manifestations such as edema (hypoproteinemia), steatorrhea (impaired lymphatic drainage leads to leakage of lymph into the intestine and malabsorption), asthenia, tetany (loss of calcium in the lymph fluid), and an immunosuppressed state (loss of lymphocytes and hypogammaglobinemia).[3]

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We report a case of CA with chylothorax who presented with recurrent episodes of unexplained pleural effusion and abdominal distention. We hope to sensitize clinicians to consider the possibility of uncommon conditions like lymphatic abnormalities when working looking for the cause of unexplained recurrent pleural effusion in a child.

Clinical Description

A 4.5-year-old girl was referred to us as a diagnostic dilemma with recurrent episodes of breathlessness and abdominal distention for a year. These episodes had not responded to treatment being given at the referral and other centers where she had sought medical attention.

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On eliciting history and reviewing whatever medical records she had, we learned that she had been apparently well until 3.5 years of age when she had experienced the first episode of respiratory symptoms. This had developed after a fever for 2 weeks' duration. The child had minimal breathing difficulty that did not interfere with her activities of daily living. There was no history of cough, coryza, or chest retractions. There were no other localizing or constitutional symptoms. The child was immunized for age, and there was no history of contact with TB.

We were unable to find any medical records of earlier examination findings during that period. However, some basic investigations for the workup of fever were available. Salient results were minimal leukocytosis (total Leucocyte count 14,200 cells/cu.mm) with Equal predominance of neutrophils and lymphocytes (45%). Platelet counts were normal (3.5 Lakhs/cumm). The C-reactive protein was elevated (42 mg/dL), and the blood culture was sterile. The chest X-ray showed right-sided pleural effusion. The Mantoux test was negative, as were the cartridge-based nucleic acid amplification tests (CB-NAAT) performed on pleural fluid and gastric aspirates (both of which were exudative as per cytology and biochemistry). She was initially managed with a short course of drugs (nature unknown), following which she was empirically started on anti-tubercular therapy (ATT) and discharged. Defervescence and resolution of right-sided effusion on a repeat X-ray were taken as a successful therapeutic trial, and she completed a course of category 1 ATT.

Regarding the current episode, she had been symptomatic for around 3 months. Abdominal distention developed 3–4 months after completing the course of ATT, followed by a recurrence of breathlessness for a month. The abdominal distention was insidious in onset and had progressively increased over 3 months. It was painless and not associated with fever, jaundice, increasing pallor, bleeding from any site, vomiting, recurrent diarrhea, greasy stools, or change in bowel habits, oliguria, or other urinary complaints. There was no history of edema of her feet or elsewhere. Fast breathing had appeared for the past month that increased in the supine and left lateral positions but displayed minimal change with physical activity or exercise. There was no history of chest pain, productive cough, or syncopal attacks. There had not been any loss of weight, though her appetite had decreased (daily intake of 1200 calories and 20 g of protein). There was no history of oral ulcers, skin rashes, or joint swellings. The child had not been exposed to any abdominal trauma or surgery in the past. She was developmentally normal and the second-born issue of nonconsanguineous parents. There was no family history of similar problems. The referral center had repeated investigations more or less on the lines of the previous approach, but was unable to find anything conclusive. A provisional diagnosis of relapse of abdominal TB was made, and she was started on category 2 ATT. The child was referred to us when she remained symptomatic despite medication.

We proceeded with the examination. She was alert and active. Vital parameters were stable; afebrile, heart rate 104/min, respiratory rate 32/min, and blood pressure 94/70 mm Hg (below 90th percentile). The weight was 16 kg (Z score 0 to −2), height 102 cm (Z score 0 to −2), and body mass index (BMI) was 15.38 (z score between 0 to +1). Pallor was present. No edema was noted in the periorbital region, sacrum, or feet. There was no icterus, clubbing, cyanosis, lymphadenopathy, petechiae, purpura, rashes, or signs of vitamin deficiencies. A Bacillus Calmette–Guérin scar was present. No abnormalities were noted in the oral cavity, skin, or joints. The respiratory system examination showed decreased air entry over the right hemithorax with stony dullness indicative of pleural effusion. Air entry was equal and vesicular in character in other areas. Abdomen examination showed a distended abdomen. There was no tenderness, guarding, or rigidity. Shifting dullness was present. The liver was mildly enlarged with a span of 10 cm. There was no other organomegaly. The cardiovascular and neurological examinations were within the normal limits.

Management and outcome

We reviewed the clinical details to ascertain the etiology of the pleural and ascitic fluid collection. The points in favor of disseminated TB (abdominal and pleural) were the prolonged but relatively indolent course of illness, initial symptomatic relief on starting ATT, presence of straw-colored pleural and ascitic fluid with an exudative nature but the absence of frank pus. However, the absence of prolonged fever, respiratory findings other than that of effusion, loss of weight, and history of contact, in the setting of negative Mantoux test (normal BMI) and CB-NAAT were against this diagnosis. Other less likely differentials were an underlying anicteric hitherto undetected liver disease, nephrotic syndrome, congestive cardiac failure, or malabsorption. However, there were no strong clinical indicators for any of these. Autoimmune disorders were also considered, but the absence of fever, joint involvement, or rashes made this possibility unlikely.

Preliminary routine tests on admission were normal [Table 1]. Routine urinalysis (including urine protein – creatinine ratio 0.2) was within the normal limits. The blood and urine cultures were sterile. The repeat Mantoux test was negative. The X-ray chest and abdomen [Figure 1] did not show any new findings. Computed tomography (CT) of the chest showed massive right-sided pleural effusion with minimal left-sided effusion and basal atelectasis. The echocardiogram was normal. Hence, cardiac, renal, hepatic, malabsorption, or nutritional pathologies were ruled out.

Since the child was afebrile, not sick, and without any other systemic manifestations despite recurrent effusions, we reviewed other possible, more uncommon causes and suspected a lymphatic malformation. Therapeutic cum diagnostic thoracic and ascitic paracentesis was performed; however, this time, it was performed in a fed state. The pleural fluid had a milky appearance. Its cytology revealed total cell counts of 2000 cells/

Table 1: Summary of preliminary investigations done at our centre (Institute of Child Health and Research Centre)

Laboratory parameter	Value	Reference range
Blood counts	WBC-9300/cumm (P-60 L 35 E 4)	4000-12,000/cumm
	Platelets-3.5 lac/cumm	1.5 L-4 L/cumm
	HB-13 g/dL	
ESR	14 mm/h	0-20
CRP (mg/dL)	2.3	0-6
Blood urea (mg/dL)	18	7-38
Serum creatinine (mg/dL)	0.6	0.3-1
Serum bilirubin (mg/dL)	0.3	0.2-1
Serum AST/ALT/alkaline phosphatase (IU/L)	25/33/156	0-40/0-40/100-300
Serum albumin (g/dL)	3.9	3.5-5
PT/aPTT	13 s/34 s (INR 1.0)	<14/34

ESR: Erythrocyte sedimentation rate, WBC: White blood cell, HB: Haemoglobin, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, PT: Prothrombin time, aPTT: Active partial thromboplastin time

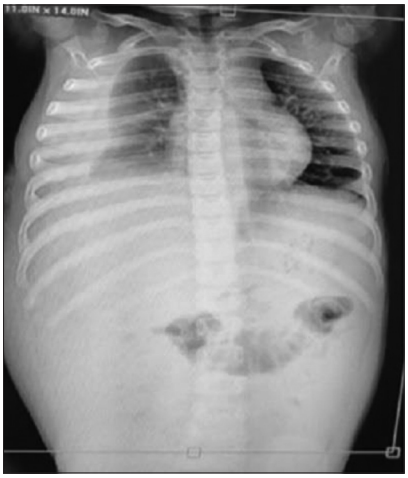

Figure 1: Right-sided pleural effusion with ascites on chest X-ray

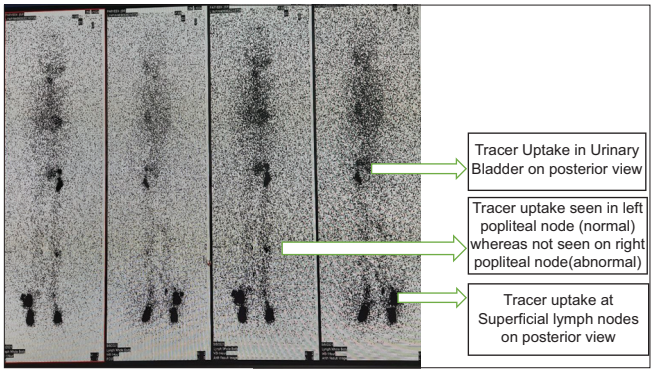

Figure 2: Lymphoscintigraphy showing no tracer uptake from right lower limb, normal uptake from left lower limb

cu.mm, of which 80% were lymphocytes. Biochemistry showed high protein (3.5 g/dL, normal 1–2 g/dL) and normal lactate dehydrogenase levels (235 IU/L, normal 100–333 IU/L). The presence of elevated pleural fluid triglyceride levels (180 mg/dL, normal <110 mg/dL) confirmed chylothorax. Ascitic fluid analysis was also suggestive of CA with high protein (3 g/dL; serum albumin: ascitic gradient <1.1 g/dL) and triglycerides (245 mg/dL, normal <200 mg/dL) levels. The cultures of Pleural and Ascitic fluid cultures were sterile. The samples were also re-investigated for TB (Tuberculosis) via CBNAAT procedure and were found to be negative: Adenosine deaminase (ADA) levels normal (pleural fluid 28 IU/L, >40 U/L indicative of TB; ascitic Fluid 30 IU/L, >36 U/L indicative of TB) and CB-NAAT negative.

A diagnostic lymphoscintigraphy was planned to rule out lymphatic abnormalities, the most common cause of chylous effusions. This showed no evidence of lymph flow from the site of injection through superficial lymphatics and diversion through deep lymphatics [Figure 2]. Tracer uptake was seen in the abdomen and urinary bladder, suggestive of microscopic lympho-venal shunts at multiple levels giving rise to CA. The urine microscopy was repeated but did not show any abnormality, indicative that the extravasation was minimal. We decided against testing it for triglyceride and chylomicron levels (that would have been confirmatory) as these specialized tests would have increased the cost without changing the management. The child was diagnosed with a case of CA with chylothorax due to lymph duct abnormalities, probably of congenital origin. She was started on a low-fat and medium chain triglycerides (MCT) rich diet.

Symptomatic improvement began gradually, and by 2 weeks, the pleural effusion and ascites had resolved. During the hospital stay, the serum albumin showed a declining trend (from 3.9 g/dL at admission to 3.6 and 3.2 g/dL over a week), probably due to minimal continuity of chylous leak. However, since she was otherwise asymptomatic, no specific treatment was planned. At discharge, we planned to consider injection of octreotide in case of recurrence of severe ascites or severe breathlessness, as per standard protocol. However, 3 months have elapsed in follow-up, and she remains symptom-free.

Discussion

Chylous ascites and chylothorax is noninfectious extravasation of a milky fluid into the respective body cavities, draining ≥200 mL/day, and has triglyceride levels of ≥110 mg/dL.[1] The etiology of CA can be classified as

follows:[4-8] traumatic or nontraumatic; portal or nonportal (based on the presence or absence of diseases affecting the portal system pressure); and congenital or acquired (inflammatory, postoperative, malignant, or infectious). Abdominal malignancy and cirrhosis are the common causes in developed countries, whereas the most causes are infectious diseases such as TB and filariasis in developing countries. A review of causes of CA listed lymphatic anomalies as the most common (32%), followed by cirrhosis (11%), mycobacterial infections (10%), and malignancy (7%).[5] The simultaneous occurrence of CA with chylothorax is a rare association above infancy. Similar cases are summarized in Table 2.[9-11]

The diagnosis of chylothorax is made by abdominal paracentesis/pleural analysis. Pleural fluid analysis in the fed state was the game changer in this case. If the patient is fed orally, the fluid has a milky appearance that otherwise appears straw colored (the probable reason for it being mistaken as tubercular in this case). Sometimes, the fluid may appear cloudy on enteral feeding. Chylous fluid is characterized by cell count of more than 500/μL (mostly lymphocytes), proteins between 2.5 and 4 g/dL, and triglycerides >110 mg/dL, with the predominance of chylomicrons. Ultrasonogram, CT, or magnetic resonance imaging of the thorax is indicated to rule out malignant (lymphoma, chronic lymphoid leukemia, and mediastinal tumors) or pre-operatively in surgical causes (i.e., tumor resection, thoracic aneurysm repair, or sympathectomy). If these investigations are not contributory, malformations of the lymphatics should be considered. The investigative modality of choice is lymphoscintigraphy[6] which involves the injection of ^{99m}Tc-dextran, sulfur colloid or human albumin into the interdigital web spaces of the feet. Laparoscopy allows to explore a magnified image of the abdominal cavity in its natural state.[6]

Table 2: Literature review and their follow up

Author (reference)	Clinical details	Follow up and outcomes
Rützel *et al*.[9]	Neonate with trisomy 21	Underwent surgery with good outcome
Bellini *et al*.[10]	33 cases with lymphatic dysplasia	Around half the cases died due to multiple congenital anomalies
George *et al*.[11]	11-month-old child with CA	Doing well on dietary interventions

CA: Chylous ascites

The treatment is primarily conservative when no surgical cause is identified. The protocol depicted in Figure 3 may be adapted for the clinical approach of such patients.[12] Chronic loss of chyle leads to anemia, hypoproteinemia, hypocalcemia, hypolipidemia, malnutrition, and an immunocompromised state, all of which are managed symptomatically as per individual protocols, keeping the underlying cause in mind. Repeated paracentesis is required to relieve symptoms. Our patient did not require repeated paracentesis since she became asymptomatic and remained the same after a single paracentesis. The primary goal is to maintain nutrition by initiating a low-fat, high-protein diet with MCT; and decreasing the production and flow of chyle. Around 50% of cases improve by this management.[7] In refractory or persistent chylothorax (absence of defervescence and resolution of symptoms within 2 weeks of starting treatment), administration of somatostatin or its analog octreotide may be considered.[7] These drugs decrease the gastric, pancreatic, and biliary secretions and

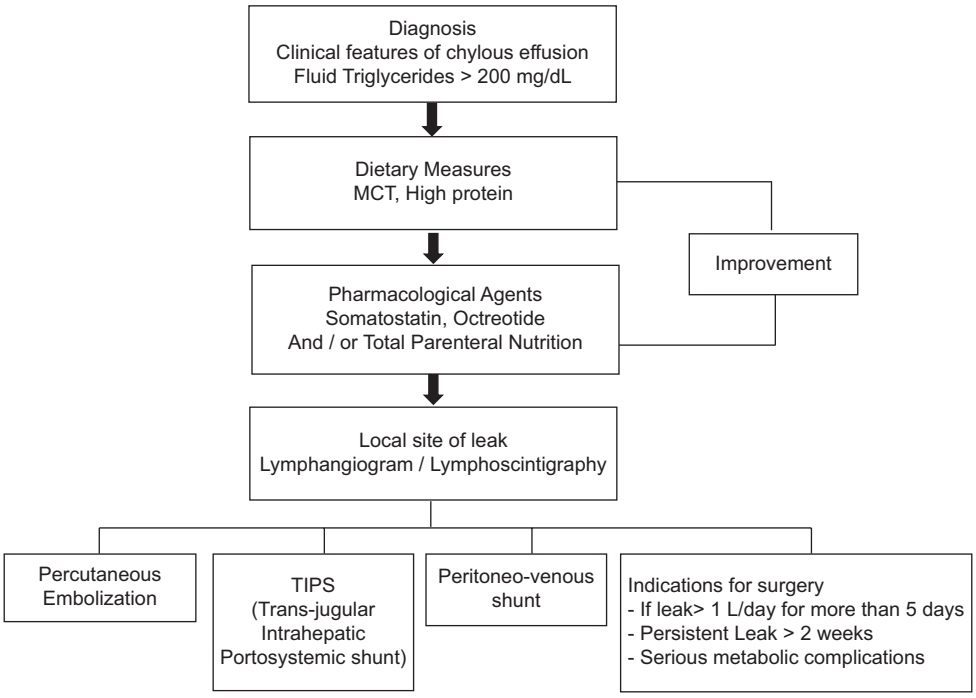

Figure 3: Algorithm for management and follow-up of patients with chylous effusions

reduce the total flow of gastric lymphatics, thereby reducing the effusions.[8] If there is no improvement within a year, surgical treatment is preferred. This includes thoracentesis, pleurocentesis, thoracic duct ligation, or embolization.[8]

To conclude, clinicians must proactively consider and exclude causes other than TB in cases of pleural effusion or ascites (even if it straw colored), if the clinical phenotype is not supported by investigations.

Informed consent

An informed consent for publication was obtained from the child's parents and has been attached to the manuscript.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Lessons learnt

- Not all straw-colored fluids (pleural/ascitic) are due to TB
- The color of chylous fluid varies from fasting to a fed state. In the latter, it appears milky
- Lymphangiography confirms the diagnosis of a lymphatic abnormality as well as helps in delineating anatomical structures in case surgery is required.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

An Unusual Cause of Recurrent Pneumonia in a Child

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Abstract

Background: Recurrent pneumonia is defined as at least two episodes of pneumonia in a year or three episodes during a lifetime, with clinical and radiological improvement in between. **Clinical Description:** A 5-year and 8-month-old boy presented with a history of three episodes of fever and fast breathing of variable duration over 8 months. In between, he had a persistent moist cough with intermittent fever, weight loss, and darkening pigmentation. He had three prior admissions for the same, with X-rays showing multilobar pneumonia. Routine investigations were normal. Tuberculosis workup was negative. Computerized tomography showed changes in consolidation without any evidence of structural abnormality. The child became asymptomatic with short courses of antibiotics and nebulization during these admissions. He was referred to us for further evaluation, and we reviewed his history, examination, and medical records. **Management:** The darkened complexion was suggestive of Addisonian pigmentation, but serum electrolytes were normal. However, very low levels of morning cortisol and high adrenocorticotrophic hormone were suggestive of adrenal insufficiency. Retrospective history revealed dysphagia with nocturnal cough suggesting aspiration. Barium swallow confirmed achalasia by the presence of a dilated esophagus with distal narrowing. The clinical phenotype was suggestive of Triple A (AAA) syndrome with Addison's disease, alacrimia, and achalasia. A positive Schirmer's test confirmed alacrimia and established the clinical diagnosis. He was started on replacement hydrocortisone and later taken up for Laparoscopic Heller Myotomy with fundoplication. On follow-up, his appetite improved, his cough subsided, he had adequate weight gain, and the pigmentation had decreased. **Conclusion:** Achalasia should be considered a differential in recurrent pneumonia. AAA syndrome has isolated glucocorticoid deficiency. Therefore, hyperpigmentation in the presence of normal electrolytes should not preclude considering the possibility of adrenal insufficiency.

Keywords: Achalasia, Addison's disease, Allgrove syndrome, recurrent pneumonia

Recurrent pneumonia is defined as the occurrence of at least two episodes of pneumonia in a year, or three episodes during a lifetime, with clinical and radiological improvement in between.[1] Depending on the number of lobes involved, recurrent pneumonia can be unilobar or multilobar. Unilobar pneumonia occurs due to either anatomical abnormalities (congenital pulmonary airway malformation, etc.), or extrinsic/intrinsic causes of airway compression (such as mediastinal lymph nodes, foreign bodies, or focal bronchiectasis). Multilobar pneumonia occurs in disorders etiologies such as primary immune deficiency, congenital heart disease, aspiration syndromes, or cystic fibrosis.

We report an unusual diagnosis in a boy who was apparently normal till 5 years of age and then presented with recurrent pneumonia, hyperpigmentation, and weight loss secondary to what emerged to be a rare genetic syndrome.

Clinical Description

A 5-year and 8-month-old boy was referred to our institute for the evaluation of three episodes of pneumonia since the age of 5 years, around 8 months. Each episode was associated with fever, fast breathing, and subcostal retractions, severe enough to require hospitalization. Documentation of examination findings during any of these events was not available. Treatment comprised nebulization with bronchodilators and intravenous antibiotics. The duration of these episodes ranged from 7–10 days before the resolution of the major respiratory symptoms, but a moist cough persisted in between the episodes. There were no associated atopic symptoms such as bouts of sneezing, nose rubbing, urticarial rashes, or allergic conjunctivitis. There was no history of snoring or open-mouth breathing at night indicative of adenoids. These symptoms had been labeled as an asthmatic cough and treated with inhaled corticosteroid and salbutamol combinations, but there was no

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significant symptomatic relief. No other contributory history was found that pointed to the involvement of any other system.

The patient was described by his parents as a happy and playful child. He had good academic performance before the illness but subsequently had frequent school absenteeism due to his illness. His appetite had decreased significantly, resulting in the loosening of clothes and a documented weight loss of around 2 kg since the onset of symptoms. His parents had also noticed generalized darkening of his complexion for the same duration.

On reviewing the previous investigations, the salient findings noted were: hemoglobin (11.3 mg/dl); normal total leukocyte count and eosinophil differential count (7600/mm^3, E 1); normal values of random blood glucose and serum electrolytes; chest X-rays done during each episode showing parenchymal infiltrates involving the left upper lobe and bilateral lower lobes, a negative workup for tuberculosis (TB) including a negative cartridge-based nucleic acid amplification of fasting gastric aspirate; and computerized tomography of the thorax (at third admission) revealing bilateral lower lobe consolidation. The patient was the second born issue of a nonconsanguineous marriage, with a healthy elder sister. There was no history of contact with TB, family history of known allergies, or suggestive of atopy. He was completely immunized and developmentally normal.

Examination revealed normal vitals: Heart rate 89/min, respiratory rate 22/min (no chest retractions), blood pressure within normal centiles, and oxygen saturation (SpO2) 97% in room air. He was undernourished with a weight of 12.6 kg (<3rd centile), the height of 108 cm (10th centile), and body mass index <3rd centile. Significant hyperpigmentation of the skin, lips, and palms [Figures 1a and b] and grade 2 clubbing were noted. There was no evidence of pallor, icterus, cyanosis, or significant lymphadenopathy. The throat was normal, and there was no sinus tenderness. On respiratory system examination, bilateral air entry was good, with scattered crepitations heard over the right infraaxillary region. There was no wheeze or other added sounds. The cardiovascular examination was normal, without cardiomegaly or murmurs. His abdomen was soft without any palpable mass or hepatosplenomegaly. There were no neurological abnormalities.

Thus, the clinical clues pointed toward a chronic disorder resulting in recurrent multilobar pneumonia, weight loss, clubbing, and skin pigmentation (that appeared typical of Addisonian pigmentation). This gave direction to our first line of investigation, rather than exploring other possibilities such as TB, allergies, and immunodeficiency disorders (that would otherwise have been likely differentials for recurrent pneumonia in a child.

Management and outcome

The routine tests conducted at our institute were normal, including random glucose (95 mg/dl) and serum electrolytes (sodium 138 meq/l, potassium 4.2 meq/l). However, the early morning cortisol level was low (1.1 µg/dl), and adrenocorticotropic hormone (ACTH) level was very high (>1250 pg/ml). A subsequent ACTH stimulation test failed to raise the cortisol levels, confirming the diagnosis of adrenal insufficiency.

We reviewed the literature for causes of recurrent pneumonia and adrenal insufficiency, and revisited the history and examination. In-depth probing revealed that the child had developed dysphagia to solids (not liquids), and that the cough occurred within minutes of lying down (suggestive of probable episodes of microaspiration). He also had occasional episodes of vomiting and regurgitation of feeds. The combination of adrenal insufficiency with dysphagia and recurrent aspiration raised the suspicion of Allgrove syndrome. A barium swallow showed dilated esophagus with distal narrowing consistent with achalasia cardia [Figure 2]. Since alacrimia is a key feature of this syndrome, we proceeded to conduct the Schirmer's test. This confirmed alacrimia since the wetting of the blotting paper was only 3 mm within the stipulated time bilaterally (normal ≥10 mm in 2 min irrespective of gender and age). The triad of ACTH-resistant cortisol insufficiency, achalasia, and alacrimia, established the clinical diagnosis of Allgrove or Triple A (AAA) syndrome in our child. We were unable to confirm this by genetic analysis due to financial constraints.

The child was started on cortisol replacement therapy in the form of oral hydrocortisone (10 mg/m^2/day) and prescribed

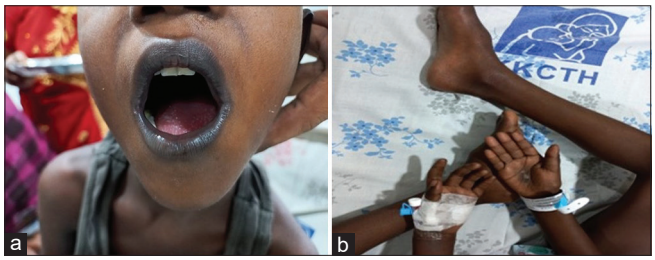

Figure 1: Hyperpigmentation involving (a) the lips; and (b) the palmar creases

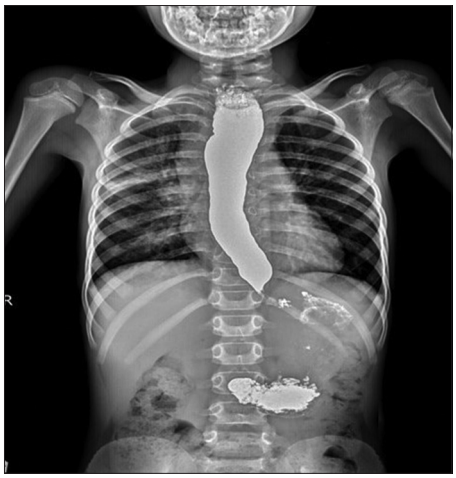

Figure 2: Moderate dilatation of the esophagus with smooth narrowing of the gastro esophageal junction-suggestive of achalasia

lubricant eye drops. After a month, he underwent laparoscopic Heller's myotomy with partial fundoplication. By his 2-month postsurgery follow-up visit, his episodes of aspiration had abated, and his appetite had improved. He displayed a gain in weight of 2 kg, and the hyperpigmentation had decreased.

Discussion

Allgrove syndrome is an autosomal recessive disorder caused by a mutation in the AAAS gene that is located on chromosome 12q. 13. This gene consists of 16 exons that encode a nuclear envelope protein known as ALADIN (alacrimia-achalasia-adrenal insufficiency-neurologic).[2] A variety of mutations are scattered throughout the gene have been reported, except exon 3. The abnormality of this protein affects the exchange of nuclear material resulting in the typical manifestations. Affected individuals develop a triad of alacrimia (90%), adrenal insufficiency (85%), and achalasia (75%), with or without associated neurological manifestations such as developmental delay and seizures.[3] Manifestations vary widely in severity, with some patients remaining asymptomatic and others displaying a fatal outcome. The classic triad is most often seen in children. Patients in whom onset is late or in adulthood will have a higher likelihood of symptoms involving the nervous system.

Alacrimia is the most common finding in AAA syndrome. Although it is present right from the newborn period, children remain asymptomatic. Even in this child, the parents remarked that the child "cried without tears" on probing but had never considered it to be something to seek medical care for. Achalasia commonly manifests in the first decade of life and is quite often the presenting symptom of this syndrome. Children manifest with dysphagia, vomiting, and weight loss. Recurrent pneumonia (as was seen in this case) occurs secondary to the stasis of food in the esophagus and subsequent aspiration. This has been described in several case reports.[4,5] We suspected achalasia when we started thinking on the lines of Triple-A syndrome. Laparoscopic Heller's myotomy, with or without fundoplication, remains the treatment of choice in children with achalasia, with excellent postoperative results.[6] Per oral endoscopic myotomy is a newer and less invasive procedure showing similar efficacy.[7] Endoscopic dilatation and Botox injection are less invasive techniques used for milder cases.

Adrenal insufficiency occurs in 85% of children with AAA syndrome that manifests during the first two decades of life. It is the leading cause of mortality in children, mainly from severe hypoglycemia and shock.[8] It should be noted that the primary cause of adrenal insufficiency in AAA syndrome is an ACTH-resistant glucocorticoid deficiency, with most children (85%) having normal mineralocorticoid production. Aldosterone (mineralocorticoid) is the principal hormone involved in electrolyte balance; hence, most children with AAA syndrome have normal electrolytes. These children have very high ACTH with low cortisol levels. Confirmation of diagnosis is by documenting the absence of cortisol elevation, post ACTH, and genetic analysis to detect the mutations.[9]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal patient identity, but anonymity cannot be guaranteed.

Lessons learnt

- Achalasia causes recurrent multilobar pneumonia due to repeated microaspiration of food particles that stagnates in the distal end of the esophagus
- Most children with AAA syndrome tend to have isolated ACTH-resistant glucocorticoid deficiency, and hence electrolytes are normal
- The classic triad of alacrimia, adrenal insufficiency, and achalasia is most often seen in children. Neurological symptoms are more common when the onset is late or in adulthood.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Acute Hemorrhagic Edema following COVID-19 Infection

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Abstract

Background: Acute hemorrhagic edema of infancy (AHEI) is an immune complex-mediated leukocytoclastic vasculitis. Despite its worrisome appearance, it has a benign disease course with rare systemic involvement. **Clinical Description:** A 25-month-old male patient was brought to the pediatric outpatient clinic with a pink oval-shaped plaque-like rash all over the body and edema on the lower extremities and left auricle. The child was diagnosed as a case of coronavirus disease 2019 (COVID-19) 5 days before the present complaints. History and physical examination were otherwise unremarkable. Because of the patient's age, the purpuric appearance of lesions, distribution pattern of the rashes, localized edema, and no end-organ involvement, a possibility of AHEI, triggered by COVID-19, was considered and the patient was evaluated for the same. **Management and Conclusions:** The patient recovered in 15 days with no end-organ involvement. He was advised to continue regular follow-ups to look for long-term complications. AHEI is a benign condition which may occur in children following COVID-19 infection. It is essential to recognize the condition to avoid unnecessary investigations and treatment.

Keywords: Coronavirus disease 2019, immune-complex, leukocytoclastic vasculitis, purpura

Coronavirus disease 2019 (COVID-19) has become a pandemic during the last 2 years. Many cases have been described in the pediatric age group with various skin manifestations such as erythema multiforme-like lesions, vesicular, maculopapular, urticarial, and papulosquamous lesions.[1] Acute hemorrhagic edema of infancy (AHEI) is an immune complex-associated leukocytoclastic vasculitis known to be a rare disease in children.[2] The age of onset is usually between 4 and 24 months. Clinical manifestations include mild fever, edema of the face and lower extremities, diffuse purpura, and ecchymosis that usually develop rapidly over 24–48 h. An association with upper respiratory tract infections and/or gastroenteritis has been reported. There are also case reports of AHEI following many vaccinations.[3,4]

In this case report, we aimed to report a pediatric case of AHEI associated with COVID-19 infection, which is rarely described in the literature. Differential diagnosis of purpuric skin lesions in children is wide and consists mostly of infectious and rheumatological diseases that require extensive investigations and treatment. Recognition of AHEI in the early course of clinical presentation can save both the patient and physician from that tiring, unnecessary and expensive process.

Clinical Description

A 25-month-old boy presented to the pediatric outpatient clinic with a pink oval-shaped plaque-like rash all over his body for 2 days. The rash started on the 5th day of COVID-19 diagnosis which was made by antigen test. The patient only had complaints of fever and mild cough before the appearance of the rash. There was no history of diarrhea, change in behavior and level of consciousness, exposure to toxic substances or drug overdose, or recent vaccination. There was no history of similar lesions in the past. On day 1 of the rash, the child was advised antihistaminics considering the possibility of acute urticaria following intake of some over-the-counter medicines but found to have no benefit.

In the present examination, vital signs revealed a body temperature of 37.0°C, respiratory rate of 24/min, mean heart rate of 95/min, and blood pressure of 100/70 mmHg. Peripheral pulses were normal and easily palpable from both the upper and lower extremities. Oxygen saturation was 99% in the right hand. His body weight was 13 kg (lying between the 25th and 50th percentile), length was 87 cm (lying between the 50th and 75th percentile), and head circumference of 48.5 cm (lying at the 50th centile). The patient was a well-nourished infant with no

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apparent respiratory distress. On general physical examination, there was no pallor, icterus, conjunctival congestion, cyanosis, or lymphadenopathy. There were widespread maculopapular, oval-shaped, plaque-like rashes on the arms, legs, face, and gluteal region, which were also present on the trunk [Figure 1]. The lesions were not blanchable regarding oppression. They were painless and nonpruritic. Edema and mild ecchymotic rashes were observed on the left big toe and on the left auricle [Figure 2]. On systemic examination, respiratory system examination revealed bilateral normal vesicular breath sounds, with no added sounds. On abdominal examination, there was no organomegaly and bowel sounds were well heard. Other systemic examinations including cardiovascular and central nervous system examinations were also normal. Henöch–Schönlein purpura (HSP) and urticarial vasculitis were considered differential diagnosis. Younger age, the nature of lesions, and the absence of other organ involvement were against the diagnosis of HSP in our case. Persistant erythematous papules and plaques and lack of treatment response to antihistamines in our case were typical for urticarial vasculitis, but lack of systemic symptoms and no itching or pain on skin lesions were points against the diagnosis of urticarial vasculitis.

Laboratory tests revealed mild leukocytosis (13840/mm3 (differential count: neutrophils: 47.1%, lymphocytes: 44%, and eosinophils: 0.42%). C-reactive protein was 2 mg/L. Coagulation parameters (international normalized ratio: 0.96 and activated partial thromboplastin time: 31.9 s), liver (alanine transaminase: 19 U/L and aspartate transaminase: 47 U/L), and renal function tests (serum creatinine: 0.4 mg/dL and blood urea: 37 mg/dL) were within normal limits for age. There was no electrolyte imbalance (sodium: 139 mmol/L, potassium: 4.2 mmol/L, and calcium: 9.3 mg/dL). On the 2nd day, the rash acquired a typical purpuric appearance, especially on the lower and upper extremities [Figure 3]. Edema and ecchymosis localized on the auricle and foot and also became more prominent. The patient's age, purpuric appearance, the distribution pattern of the rashes, edema involving the auricle and foot, and the absence of end-organ involvement were indicative of a diagnosis of AHEI, triggered by COVID-19. Histopathologic examination of skin lesions was unavailable in our hospital setting, so a clinical diagnosis of AHEI was made with the above findings. Diagnosis of AHEI is majorly based on clinical grounds. In doubtful cases, the skin biopsy may be of great value for diagnosis.[2] The parents were counseled about the expected course of the disease. In outpatient follow-up, rashes and edema disappeared on the 15th day.

Figure 1: Maculopapular rashes on upper, lower extremities and trunk

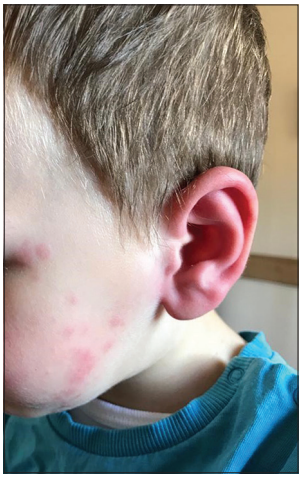

Figure 2: Edema and ecchymosis on left auricle

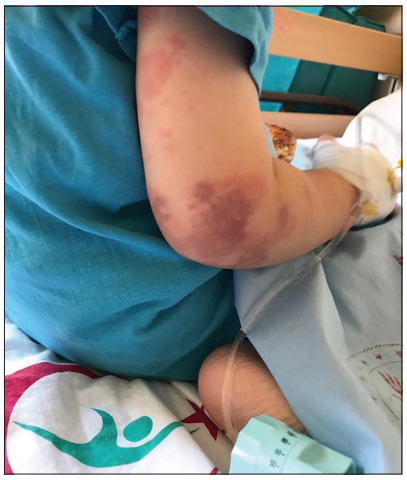

Figure 3: Purpuric lesions on the left upper extremity

Discussion

AHEI is classically characterized by rapidly developing purpuric lesions involving the face, extremities, and bilateral auricles. The appearance of bilateral auricular edema and purpura in a well, nontoxic child should raise clinical suspicion of AHEI.[5] Extracutaneous manifestations may develop in <10% of patients. Glomerulonephritis, abdominal pain, arthralgia, testicular torsion, and invagination are some of these findings.[6] The diagnosis is made mainly on the basis of clinical findings and skin biopsy is generally not required.

Table 1: Coronavirus disease 2019-associated acute infantile hemorrhagic edema cases in literature

	Age (months)	Initial presentation	Clinical course	Systemic involvement
Case 1	14	Fever and vomiting, rashes appear on 9th day of COVID-19 diagnosis	Full recovery on 14th day of AHEI diagnosis	No systemic involvement
Case 2	20	Fever, mild cough, progressive purpuric/ecchymotic lesions, and extreme swelling in the past 2 days, COVID-19 infection is detected on first presentation	Full recovery on 5th day of AHEI diagnosis	No systemic involvement
Case 3	10	2 days of fever and purpuric rash, father was diagnosed with COVID-19 7 days ago	Full recovery on 21th day of AHEI diagnosis	No systemic involvement
Case 4 (our case)	25	Fever, mild cough, urticarial and purpuric rash on 5th day of COVID-19 diagnosis	Full recovery on 15th day of AHEI diagnosis	No systemic involvement

COVID-19: Coronavirus disease 2019, AHEI: Acute hemorrhagic edema of infancy

If a biopsy is performed, IgA deposition can be expected in one-third of the patients by immunofluorescent staining. Histopathologic findings are compatible with leukocytoclastic vasculitis.[7] Laboratory tests do not reveal any disease-specific findings. Leukocytosis, thrombocytosis, increased CRP, and sedimentation rate may be observed.[8]

AHEI has been reported after specific infections including tuberculosis, Coxsackie virus, *Campylobacter*, rotavirus, hepatitis A virus, cytomegalovirus, and pneumococcal bacteremia.[3,8] It has also been reported after many vaccinations. In a literature review of 195 AHEI case reports, 18 children developed AHEI in <15 days after immunization, including combined vaccination against diphtheria, pertussis, and tetanus with pr without poliomyelitis, combined vaccination against measles, mumps, and German measles; concurrent vaccination against measles, mumps, German measles, and chickenpox; and isolated vaccination against *Haemophilus influenzae* type B, measles, tuberculosis, or smallpox.[8] Cases of AHEI have also been reported after the influenza vaccine.[4]

AHEI may be confused with urticarial vasculitis in appearance but can be differentiated based on clinical features. Urticarial vasculitis is often associated with pruritus and the presence of systemic features such as arthralgia, lymphadenopathy, and abdominal pain.[2]

The appearance of AHEI can also resemble HSP.[9] The rash in HSP is in the form of palpable purpura starting as pink macules and developing into petechiae or larger ecchymoses mainly in children between 3 and 10 years. HSP skin lesions are usually symmetric and occur in the gluteal region, lower extremities, and on pressure points. Musculoskeletal, gastrointestinal, renal, and neurologic manifestations are common in HSP. Unlike the rash of HSP, which is usually smaller in size, the rash in AHEI appears as ecchymotic changes, large purpuras, and edema and involves the face, extremities, and scrotum.[10] In our patient, clinical differentiation was made considering these differences.

A large number of skin lesions have been reported in association with COVID-19 infection. In a systematic review that examined the dermatologic manifestations of COVID-19 in children, chilblain-like lesions were the most common cutaneous manifestation in children and adolescents (67.5% of patients). The erythema multiforme-like lesions affected 31.7% of patients and the varicella-like lesions to 0.8% of cases.[11] Chilblain-like lesions, also known as COVID toes, are well-described dermatoses characterized by erythema and swelling localized to acral areas, occurring most commonly on the toes and fingers.[8-15] The second-most common cutaneous manifestation related to COVID-19 was erythema multiforme-like lesions. Erythema multiforme is an acute, self-limited, manifestation that is considered to be a type IV hypersensitivity reaction. Lesions often start on the extremities and evolve into the pathognomonic target or iris lesions, within a 72-h period.[11,12] AHEI has also been reported in association with COVID-19.[13-15] AHEI develops as a result of endothelial damage.[12] To the best of our knowledge, the number of cases of AHEI that have been shown to be triggered by COVID-19 has been very limited in the literature.[13-15] All cases, as in our case, showed complete recovery without any organ involvement [Table 1]. Acute infantile hemorrhagic edema is a self-limiting disease that usually resolves without the need for treatment. It is also important to be aware that this picture may also occur in children followed up for COVID-19 to avoid unnecessary investigations and treatments in the follow-up of patients.

Lessons learnt

- COVID-19 infection may present with various skin lesions in children. Differential diagnoses are wide and should be cautiously evaluated.
- Acute hemorrhagic edema of infancy is a leukocytoclastic vasculitis usually related to infections and vaccinations, its diagnosis is mainly clinical and disease course is usually benign.
- Acute hemorrhagic edema of infancy should be distinguished from urticarial vasculitis, Henoch–Schonlein Purpura (IgA Vasculitis), and drug eruptions.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients

understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Neonatal Purpura Fulminans by an Unusual Pathogen: *Elizabethkingia meningoseptica*

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Abstract

Background: Neonatal purpura fulminans (PF) is a rare disorder characterized by the formation of dermal microvascular thrombosis associated with disseminated intravascular coagulation (DIC). It can be caused by inherited protein C or protein S deficiency or severe sepsis with DIC due to organisms such as *Streptococcus pneumoniae* and Gram-negative bacteria. **Clinical Description:** A preterm boy of 31-week gestation and weighing 1480 g was delivered by cesarean section. There were no risk factors for sepsis. He presented with respiratory distress after birth, was shifted to the neonatal intensive care unit (NICU), was diagnosed as respiratory distress syndrome, and was managed as per standard protocol. **Management:** On the 6th day of life, the neonate developed pulmonary hemorrhage, multiple purpura on his upper and lower extremities, and shock. Raised D-dimer (>400 ng/ml), increased prothrombin and activated partial thromboplastin time, and thrombocytopenia (6000/μL) were indicative of DIC. The blood culture isolated *Elizabethkingia meningoseptica*. Meningitis was ruled out. Supportive care included fresh frozen plasma and platelet transfusion, antibiotics as per drug sensitivity, and granulocyte colony-stimulating factor. The baby improved and the lesions healed with scarring. Protein S and protein C deficiency was excluded on follow-up. On follow-up, at corrected age of 6 months, the baby was developmentally normal. Three additional cases were identified in the unit around the same time, however outbreak investigation could not identify origin of the pathogen. **Conclusion:** We could not find any earlier publications of neonatal PF due to *E. meningoseptica* septicemia. This organism is a cause of sepsis and meningitis in preterm babies and outbreaks in NICU settings. Early identification, meticulous assessment, and prompt specific antimicrobial treatment are important for survival.

Keywords: Disseminated intravascular coagulation, protein C, protein S, thrombohemorrhagic

Neonatal purpura fulminans (PF) is a rare thrombohemorrhagic disorder associated with disseminated intravascular coagulation (DIC) in neonates and characterized by the formation of dermal microvascular thrombosis.[1] There are three types: neonatal (due to mutations of genes encoding for protein C or protein S), acute infectious, and idiopathic.[2] The underlying causes may be genetic or acquired. The latter are more common and often associated with acute fulminant sepsis caused by Gram-negative organisms, *Staphylococcus* species, *Streptococcus*, and *Neisseria meningitidis*.[2] This results in consumptive coagulopathy and transient relative deficiency of protein C and/or S.[1] Multiorgan involvement may occur due to thrombosis of both small and large vessels which leads to high mortality and morbidity.[3]

We report a case of neonatal PF with DIC due to *Elizabethkingia meningoseptica* infection. To the best of our knowledge, we report the first case of PF due to *E. meningoseptica*.

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Clinical Description

A preterm boy of 31-week gestation and weighing 1480 g, appropriate for gestational age (AGA), was delivered by cesarean section (in view of fetal distress). The mother was a 33-year-old multigravida with a previous live issue (a 3-year-old girl) and one abortion. The present pregnancy was by natural conception but had been complicated by pregnancy-induced hypertension and gestational diabetes from the 22nd week of gestation onward, for which she was on labetalol, oral acarbose, and insulin injections. The antenatal ultrasounds performed at 19 and 26 weeks were normal.

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The mother received two doses of betamethasone (12 mg) 24 h apart, 2 days before delivery. There was no history of any risk factors for early-onset sepsis such as leaking per vaginum, maternal fever, and prolonged rupture of membranes. APGAR score was 7 and 8 at 1 and 5 min, respectively. The baby displayed signs of respiratory distress with a Silverman–Anderson score of 4/10. He was shifted to the neonatal intensive care unit (NICU) for initiating continuous positive airway pressure (CPAP) and preterm care.

At admission, the baby had a heart rate of 140/min with normal volume pulses, capillary filling time of <3 s, respiratory rate of 76/min associated with nasal flaring, upper chest and xiphoid retraction, and grunt audible with stethoscope. The settings of CPAP were set to maintain a target saturation of 90%–95%. Minimally invasive surfactant therapy technique was initiated at 30 min of life as the oxygen and pressure requirement persisted, and CPAP continued. After surfactant therapy, the condition of the baby gradually improved, with a decrease in oxygen requirement and CPAP pressure. At 6 h of life, the baby was on minimal CPAP support [21% FiO2 (fraction of inspired oxygen) and Positive end-expiratory pressure (PEEP) of 4], the baby had a heart rate of 136/min, capillary filling time <3 s, mean blood pressure was 34 (56/26) mmHg, and both femoral pulses were well felt. The abdomen was soft, with peristaltic sounds present on auscultation. The tone was normal for his gestational age. The baby weighed 1480 g (between the 10th and 50th centiles), his head circumference was 30 cm (between the 50th and 90th centiles), and his length was 41 cm (between the 10th and 50th centiles). The baby was diagnosed clinically as preterm, very low birth weight (VLBW) with respiratory distress syndrome.

Management and outcome

Empiric antibiotics were started after taking sepsis screen and blood culture. Minimal enteral feeds were initiated at 6 h of life and gradually graded up. At 30 h of life, the baby developed poor circulation and worsening respiratory distress with increased O2 requirement. He was intubated and mechanical ventilation started. Preliminary reports revealed hemoglobin – 16.5 gm%, total leukocyte count – 12300/mm^3, platelet count – 2.3 lakh/mm^3, and C-reactive protein (CRP) – 4.2 mg/L. Bedside echocardiogram screening revealed a 3-mm hemodynamically significant patent ductus arteriosus, which was treated with intravenous paracetamol. After initial improvement in perfusion, and decrease in ventilator requirement on days 3–5, the baby developed pulmonary hemorrhage on the 6th day of life, followed by shock. Multiple well-demarcated bluish patches (identified as purpura) were noted on both upper and lower limbs [Figure 1], which progressively increased over the next 24 h. The centers of the lesions became necrotic and multiple patches developed over the feet, legs, and hands, the largest one measuring 3.5 cm × 3 cm over the left foot.

A clinical diagnosis of PF was suspected. Pulmonary hemorrhage and shock were managed with ventilatory support, fresh frozen plasma (FFP) transfusion, injection Vitamin K, and dopamine infusion. A repeat sepsis screen showed fall in hemoglobin to 6.9 g/dl, leukopenia (total leukocyte count: 3020/µl) with neutropenia (absolute neutrophil count: 262/µl), thrombocytopenia (platelet count: 6000/µl), and increase in CRP (9 mg/L). Biomarkers for DIC were raised: D-dimer levels >400 ng/ml (normal <200 ng/ml) and prothrombin time (20.4 s, INR: 1.6) with activated partial thromboplastin time 56 s (reference range: 26–42). Fibrinogen levels could not be done due to logistic reasons. Ultrasonographic (USG) color Doppler of the large vessels of the upper and lower limbs showed no evidence of thrombosis. The USG of the cranium and abdomen for asplenia was normal. The blood culture grew *E. meningoseptica* that was sensitive to levofloxacin and vancomycin, and the antibiotics were modified accordingly. Colony-stimulating factor (CSF) analysis (27 cells with 90% lymphocytes, protein: 87 mg/dl, and sugar: 55 mg/dl) including sterile culture excluded meningitis.

The baby was given supportive management in the form of high-frequency oscillatory ventilation for the pulmonary hemorrhage, FFP, packed cell and platelet transfusion, and granulocyte-CSF injections (for neutropenia). The margins of the purpurae gradually showed well-defined demarcation over the next 3 days. Scab formation was seen over the following 7 days, with scar formation within 3 weeks. Antibiotics were continued for 14 days. The baby was discharged on full oral feeds at 36 days of life at a corrected gestational age of 36 weeks with a weight of 1680 g.

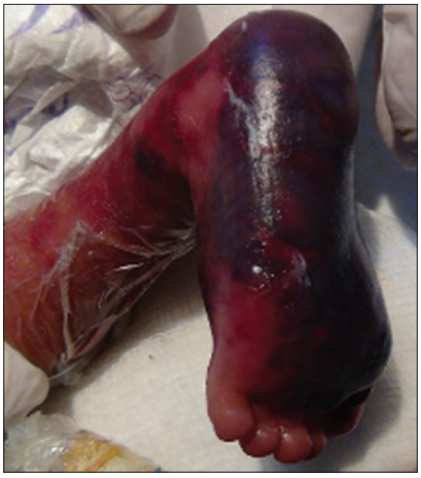

Figure 1: Cutaneous necrosis involving foot

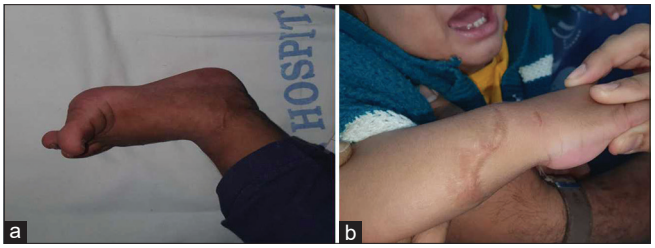

Figure 2: Healing with scar on follow-up (a) foot, (b) scar over wrist and hand

The baby was kept under close follow-up. The lesions had evolved into depigmented macules by 2 months of age [Figure 2a and b]. We also got protein C and protein S levels, done, to rule out genetic causes of PF, which were normal. Galactosemia was ruled out as part of newborn screening. Three more cases of *E. meningoseptica* were identified during same time; as per standard protocol an out break investigation was carried out, however, the source of infection could not be localized. All the cases were preterm, VLBW neonates presenting with late-onset sepsis and neonatal seizures. Two of them had concurrent CSF culture-proven meningitis.

Discussion

Clinicians should keep a high index of suspicion of PF in young infants with purpuric and necrotic lesions. This condition may occur due to inherited mutations of the genes encoding protein C and/or protein S, galactosemia, or acquired causes such as severe sepsis, DIC, severe hepatic dysfunction, antiphospholipid antibodies, or warfarin therapy.[1] It is a hematological emergency in which skin necrosis and DIC may progress rapidly to multiorgan failure caused by thrombotic occlusion of small- and medium-sized blood vessels.[3] Management is based on clinical and laboratory findings. Supportive therapy with blood component therapy should be given to maintain the platelet count >50,000 × 10^9/L and the fibrinogen level >1 g/L. Specific management depends on the cause. In congenital protein C and S deficiency, the acute phase of replacement therapy should be followed by maintenance therapy and anticoagulation with warfarin. Severe infection is treated by appropriate intravenous antibiotics.[1] Early lesions are reversible with timely intervention, though established lesions often progress to full-thickness skin necrosis within 24–48 h and may require surgical debridement, fasciotomies, or even amputation.[3] PF is associated with more than 50% mortality rate in children and often major long-term morbidity like amputation of the limb, blindness, and cerebral palsy in those who survive, emphasizing the importance of early and aggressive treatment in such conditions.

There are a few case reports of PF due to *Streptococcus, Acinetobacter*, and *Citrobacter* sepsis.[2,4] To the best of our knowledge, PF due to *E. meningoseptica* has not been reported earlier. *E. meningoseptica* formerly known as *Chryseobacterium meningosepticum* is a nonmotile, Gram-negative bacillus found mostly in soil and fresh water that causes severe infection in immunocompromised patients.[5] It causes neonatal meningitis, especially in premature infants during the 1st week of life. Other manifestations include bacteremia, pneumonia, cellulitis, septic arthritis, and urinary tract infection.[6,7]

This organism has become a potential source of infections in the hospital environment. It can survive in chlorine-treated municipal water supplies, often colonizing sink basins and taps.[8] It has also been isolated from chlorhexidine gluconate solutions that are used in hospital wards for hand hygiene.[9] *E. meningoseptica* can present with skin manifestation apart from sepsis and meningitis in premature low birth weight infants in NICU. Ghafur *et al*. reported 29 cases of *E. meningoseptica* sepsis from a hospital in Chennai, India, out of which 11 cases were in immunocompromised hosts such as stem cell transplant and malignancy patients.[10] A recent review in 2017 included 283 published cases of *E. meningoseptica* infections in children and neonates, of which 35 cases were from India and more than three-quarters (215 out of 283 cases) were in neonates.[6] As *E. meningoseptica* can cause an outbreak of sepsis, can survive in water source for a long time, and is difficult to treat, a thorough outbreak investigation in NICU is important. In our case, we sent a culture of swabs from ventilator used, NICU incubator, suction bottle, air conditioner, tap water used for handwashing, distilled water used for humidifier, parenteral nutrition used for the patient, and mother's breast milk.

This organism may be a future threat in NICU due to its multidrug-resistant nature. We report this case to emphasize the importance of prompt diagnosis, early recognition of organism, specific antibacterial treatment, and outbreak investigation in a NICU setting.

Lessons learnt

- Appearance of well-demarcated skin lesions with central necrosis in preterm septic neonates, PF should be suspected
- *E. meningoseptica* should also be considered a cause of PF besides the usual organisms, especially in PT infants
- PF can present with multiorgan failure and skin necrosis and can have long-term morbidity. Hence, early identification and aggressive treatment is important for prevention of mortality and morbidity.

Acknowledgment

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Neonatal Scrub Typhus with an Eyelid Eschar Masquerading as "Late-onset Sepsis"

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Abstract

Background: Scrub typhus is a mite-borne infection caused by the bacterium, *Orientia tsutsugamushi*. It is re-emerging in many parts of South East Asia, particularly in rural India. Although no age group is immune to this infection, scrub typhus in neonates is rarely suspected and reported. Here, we report a neonate with scrub typhus who was initially misdiagnosed as "late-onset neonatal sepsis." **Clinical Description:** A 26-day-old exclusively breastfed infant presented with fever, vomiting, loose stools, abdominal distension, and refusal of feeds for 3 days. Examination revealed an irritable, febrile, and pale infant. She had tachycardia and facial puffiness. On abdominal examination, generalized distension with hepatosplenomegaly was noted. Blood investigations were suggestive of lymphocytic leukocytosis, thrombocytopenia, toxic granules in peripheral smear, and elevated C-reactive protein. **Management:** The infant was promptly started on empirical antibiotics for "late-onset sepsis." However, in view of poor response, other possible differential diagnoses were considered. Careful reexamination revealed a necrotic ulcer covered by a yellow scab with erythematous rim on the left lower eyelid. Based on the clinical presentation and an eschar-like lesion, scrub typhus was suspected. The neonate was started on oral azithromycin and immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) testing for scrub typhus came back positive. Fever subsided immediately within 48 h and the infant was discharged after 7 days. **Conclusion:** Acute febrile illness due to scrub typhus can affect newborns. A high index of suspicion is required for early diagnosis. Timely treatment leads to prompt clinical response and reduced complications.

Keywords: Chigger, eschar, febrile illness, neonate, newborn

Scrub typhus is a re-emerging, tropical zoonosis, transmitted by chiggers, the larval stages of trombiculid mites belonging to *Leptotrombidium* species. The causative organism, *Orientia tsutsugamushi*, enters the host through a chigger bite which later evolves into an eschar, a necrotic lesion in the skin at the site of chigger bite.[1] Children of all age groups are at risk of developing this infection, but neonatal cases of scrub typhus are rarely reported.[2,3]

A high index of suspicion is needed in young infants. Delayed diagnosis can be complicated by end-organ failure and increased mortality.[2] When diagnosed early and treated on time, scrub typhus responds well to antimicrobials, such as azithromycin or doxycycline.[4] We report a case of neonatal scrub typhus which is relatively rare and was misdiagnosed as "late-onset sepsis" due to its nonspecific clinical presentation.

Clinical Description

A 26-day-old girl was brought to the casualty with complaints of fever for 3 days, vomiting with loose stools for 2 days along with abdominal distension, and refusal to feed for 1 day. The neonate initially developed vomiting, which was acute in onset, 6–8 times/day, mostly after feeds, nonbilious, and nonprojectile. Loose stools were 10–12 episodes/day, yellow, not associated with blood or mucus, and associated with abdominal distension. The urine output was decreased, but not associated with crying after micturition, dribbling of urine or any blood, or pus noted per urethra. The refusal of feeds was associated with lethargy. The baby was exclusively breastfeed and there was no history of progressive paleness, yellowish discoloration of eyes or body, any skin lesion, or any harmful child-rearing practices such as bottle feeding, top milk feeds, ghutti or water intake, or oil instillation in the nose/mouth.

She was the first issue of nonconsanguineous parents, delivered at term gestation by normal delivery following an uneventful antenatal period. She cried immediately at birth and her birth

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weight was 3.2 kg. There were no significant perinatal events and she was discharged on the 3rd day of life.

At admission, she was febrile (axillary temperature 39°C) and had a pulse rate of 166/min with normal perfusion (blood pressure of 86/60 mm of Hg). Her respiratory rate was 46 breaths/min and saturation at room air was 96% on the right hand. Her anthropometric measures were within the normal range as per the WHO percentile chart for girls, with a weight of 3.8 Kg (50th–15th percentile), length of 52 cm (50th percentile), and head circumference of 36.5 cm (50th percentile). On examination, she was irritable and pale with bilateral periorbital puffiness but no eye discharge. There were no associated findings such as jaundice, maculopapular skin rashes, and dependent edema at any other site or sclerema.

Abdominal examination revealed nontender and diffuse abdominal distension with hepatosplenomegaly (liver 2.5 cm below the right costal margin, with a span of 7 cm, and spleen 3 cm below the left costal margin, in the axis of the 10th rib). Bowel sounds were normal. The anterior fontanelle, cry, activity, spontaneous movements, tone, and neonatal reflexes were within normal limits. Examination of the cardiovascular and respiratory systems was noncontributory. Based on the clinical presentation, late-onset sepsis with the possibility of meningitis, gastroenteritis, or urinary tract infection was suspected.

Management and outcome

The neonate was treated with supportive therapy and injectable antibiotics (cefotaxime and amikacin). The preliminary hemogram revealed anemia (hemoglobin –10.4 gm%), leukocytosis (total leukocyte count –14,700 cells/mm^3), normal differential leukocyte count (35% polymorphs, 61% lymphocytes, and 4% eosinophils), and thrombocytopenia (platelet count –98000 cells/mm^3). The C-reactive protein was 60 mg/dL (normal <6 mg/dL) and micro erythrocyte sedimentation rate (micro-ESR) (1 h) 30 mm. The peripheral smear showed toxic granules. Results of other laboratory tests such as blood sugar, electrolytes, liver function, and kidney function tests were within normal limits. Lumbar puncture was not done due to low platelet count. The urine routine and microscopy examination were within normal limits.

Supine abdominal X-ray did not reveal any dilated bowel loops, bowel wall edema, or features suggestive of pneumatosis intestinalis. The ultrasound of the abdomen showed free fluid with hepatosplenomegaly. Cranial ultrasound and echocardiography were normal. Rapid malarial test and dengue serology were negative. The blood and urine cultures were sterile.

In spite of 48 h of therapy, the fever and refusal of feeds persisted. On re-examination, we noted a shallow ulcer covered by a yellow scab with erythematous rim on the left lower eyelid [Figure 1]. This had not been evident at admission due to the puffy eyelids. This led us to suspect scrub typhus. On probing, we elicited the history of the mother placing the baby on bare ground without using a sheet while she cooked outside the house. She also had a habit of drying the washed clothes on the surrounding scrub vegetation, instead of using a clothesline.

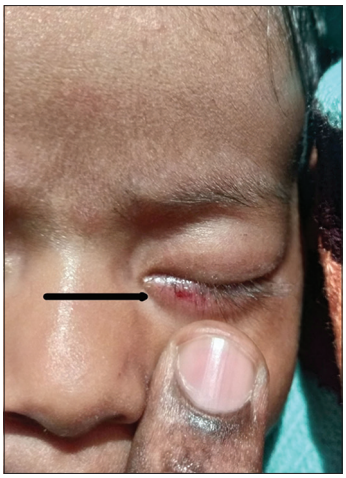

Figure 1: Atypical eschar on the left lower eyelid (black arrow)

The neonate was started on oral azithromycin after sending immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) for scrub typhus. The fever reduced and the baby started breastfeeding well within 48 h. The IgM ELISA for scrub typhus was positive with an optical density (OD) value of 1.92 (normal is <0.5 OD). Within the next 2 days, the eyelid edema subsided, hepatosplenomegaly regressed, and the platelet count normalized. She was discharged after 7 days of therapy.

Discussion

Scrub typhus is a re-emerging infection causing acute febrile illness in children. The initial presentation is nonspecific and mimics other common tropical infections such as sepsis, dengue fever, malaria, enteric fever, and pneumonia, particularly in younger children.[4]

Most neonatal scrub typhus presents with features of "late-onset sepsis," whereas severe cases may even present with shock and respiratory failure.[3] The diagnosis is often missed as the eschar, which is a pathognomic sign of scrub typhus, is less commonly seen in neonates.[5] The eschars are commonly seen in the anatomical folds of the groin and axilla. Its occurrence on the face is uncommon and involvement of the eyelid is rare.[5,6] A case of eyelid eschar has been reported in a 5-year-old child who presented with fever and eyelid swelling.[6]

IgM ELISA is a commonly used serological test for confirming the diagnosis. This becomes positive only after 5–7 days of the onset of fever. Thus, a high index of suspicion in the 1st week of infection should be based on clinicolaboratory findings.[7] Doxycycline is preferred over azithromycin in the treatment of scrub typhus due to its swift response without any adverse effects.[8,9] Defervescence usually occurs within 48 h (as seen in this case), although delayed fever clearance can be expected in severe cases with organ dysfunction.[10,11]

Apart from rodent control, prevention of exposure to chiggers can prevent the acquisition of scrub typhus, especially in rural areas.[12] Outdoor cooking has been considered a modifiable behavioral risk factor for acquiring scrub typhus. This provides a favorable environment for both chiggers and rodents.[12] Similarly, drying washed clothes on scrub vegetation, a common practice in rural India, has been found to increase child-chigger contact. The use of a clothesline would be an effective protective measure.[12] To conclude, scrub typhus should be considered a differential diagnosis in any neonate presenting with features of sepsis, particularly in endemic areas. History regarding behavioral risk factors for acquiring scrub typhus along with the search for eschar should be elicited in all suspected cases.

Lessons learned

- Although rare, scrub typhus can affect young infants, especially in endemic areas
- Neonatal scrub typhus should be considered a differential diagnosis of late-onset sepsis
- In suspected cases, diligent examination to look for an eschar should be undertaken
- Treatment is started empirically without waiting for the serology result.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Giant Primary Cerebral Hydatid Cyst

A previously healthy 11-year-old female child presented with a progressively increasing headache for 15 days. There was no history of ataxia, nystagmus, and weakness. There were no visual problems or chronic upper respiratory problems indicative of sinusitis. Examination revealed the absence of hypertension, bradycardia, and abnormal breathing pattern. The Glasgow Coma Scale was 15/15. There were no significant neurological findings apart from the bilateral 6th nerve palsy. The fundus was normal. Systemic examination was normal. A magnetic resonance imaging of the brain was planned considering a structural central nervous system lesion.

The magnetic resonance imaging revealed a large (42 mm × 39 mm × 42 mm), well-defined, cystic lesion in the left frontal lobe, with a regular wall and collapsed intra-luminal membrane. Surrounding white matter edema, mass effect with herniation, and right ventricular dilatation were noted [Figure 1]. The primary radiological differential diagnosis was a cerebral hydatid cyst. Additional investigations like a chest X-ray and abdominal ultrasonogram excluded hydatid cysts elsewhere at other likely sites. The IgG anti-Echinococcus antibody titres were normal. The intact cyst was removed surgically [Figures 1a and b and 2] using the Dowling technique, followed by oral Albendazole as per standard protocol. Histopathology confirmed the diagnosis. The child was discharged uneventfully, is on follow-up and is asymptomatic.

Hydatid disease is caused by Echinococcosis, the larval stage of a tapeworm *Echinococcus granulosus*.[1] Humans get infected accidentally through Feco-oral route via direct contact with an infected dog. Four species infect humans with the respective presentations: *E. granulosus* (cystic echinococcosis), *Echinococcus multilocularis* (alveolar echinococcosis), *Echinococcus oligarthus*, and *Echinococcus vogelix* (polycystic hydatid disease). The most common affected sites are the liver (75%) and lungs (15%) followed by the spleen, kidney, heart, bones, and brain (10%). Brain hydatid cysts can be primary (single) or secondary (multiple). Clinical manifestations are usually due to elevated intracranial pressure and/or mass effect. Focal neurological deficits may occur depending on the location and size. Definitive diagnosis is by detection of IgG anti-Echinococcus antibodies using enzyme-linked immunosorbent assay (though titers are low or absent in isolated cysts), or histopathology. The Dowling Orlando technique is the most effective surgical method for the removal of cerebral hydrated cysts with minimal risk of rupture.[2] In this technique, the head is placed lower than the level of the operation table and the craniotomy flap is opened according to the size and site of the lesion. The surgical field must be cleaned with scolicidal solution (warm 3% normal saline solution) to prevent recurrence because even a minimal spillage can lead to new cysts formation, i.e. 1 mL of cyst fluid contains 4,000,000 scolices. Concurrent high-dose glucocorticoids minimize the inflammatory response. Presurgical administration of benzimidazoles such as Albendazole or Mebendazole reduces the rate of recurrence, and the medication should continue for 6 months.

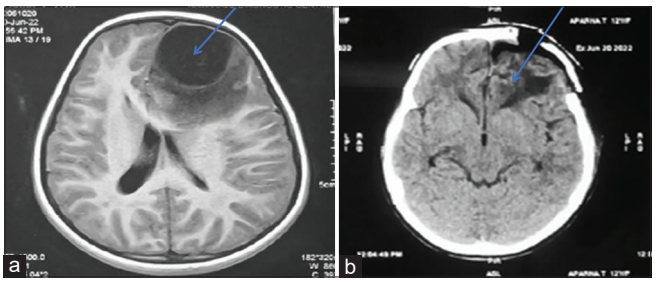

Figure 1: (a and b) Shows Preoperative MRI Brain which shows a large CSF density cystic lesion on the left side causing mass effect and midline shift to the right. Postoperative CT scan showed a large space without any residual matter. MRI: Magnetic resonance imaging, CT: Computed tomography, CSF: Cerebrospinal fluid

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parent has given his consent for images and other clinical information to be reported in the journal. The patient's parent understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

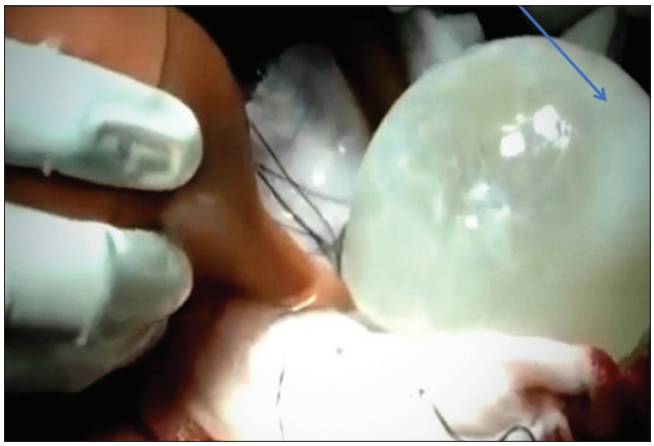

Figure 2: This shows the cyst removed in toto after operation. The cyst appears creamy and smooth

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Neonatal Genital Trauma Following Breech Delivery

A baby girl of 39^{+5} weeks gestation was born to an unsupervised second gravida mother by breech vaginal delivery after 8 h of labor. The Apgar score was normal (7 and 9 at 1 and 5 min, respectively) and birth weight 2.8 kg. At birth, the baby had transient tachypnea which settled within 6 h. Genital swelling and discoloration were also noted which was not associated with excessive irritability and/or crying when she passed urine. Breastfeeding was established successfully. The vitals were stable. Local examination revealed tender swelling of the labia which was bilaterally symmetrical, smooth, and violet red in color [Figure 1a]. The surrounding structures were normal. The rest of the general physical and systemic examination was unremarkable. We kept a diagnosis of postdelivery genital trauma and monitored the baby for complications.

At 30 h of life, the baby developed neonatal jaundice. Although investigations revealed Rh-incompatibility, the jaundice was not considered pathological since the need for phototherapy resolved within 24 h. The swelling and ecchymosis diminished spontaneously by 7 days of life without any complications, and she was discharged on the 8th day, after which she remained asymptomatic. Figure 1b was the status at 3 months.

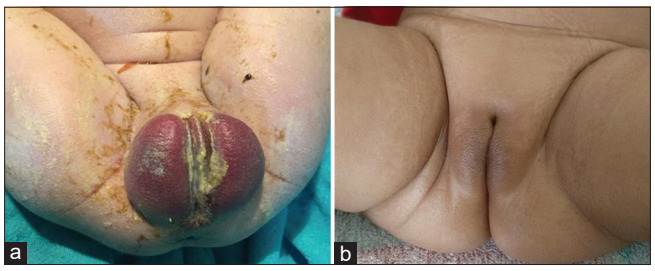

Figure 1: (a) Diffuse hematoma of labia majora at birth. (b) Complete resolution of hematoma without sequelae at 3-month of age

The initial differential diagnoses of bilateral labial swelling with or without discoloration are genital trauma, ambiguous genitalia, congenital genital hemangioma, inguinal hernia, and infections. Detailed history and careful examination is crucial to determine the underlying cause as it prevents unnecessary investigations. Genital trauma is a known complication of breech delivery. It can range from mild labial swelling in females to testicular torsion in males. Leakage from capillaries and venules during labor lead to diffuse ecchymosis which result in swollen and tender genitalia.[1] Most cases are asymptomatic with uneventful resolution within a week, but some babies may experience mild perineal discomfort and pain on micturition. Some neonate may develop neonatal jaundice due to the breakdown of red blood cells on resorption of the hematomas.[1] Ambiguous genitalia can result from virilization of the genetic female (labial hypertrophy and clitoromegaly) or under-virilization of the genetic male (bifid scrotum, micropenis, and perineal hypospadiasis).[2] In this case, only the labia majora appeared transiently hypertrophic at birth due to the swelling, and the clitoris and labia minora were normal. Congenital hemangiomas present at birth and starts involuting within weeks with complete resolution by 6-14 months. Inguinal hernia in baby girls may present as an intermittent labial bulge during crying, coughing and straining, when there is increased abdominal pressure.[3] Perianal streptococcal infection, candidal diaper dermatitis, and Bartholin gland abscess may have a similar appearance but usually can be differentiated clinically.

Declaration of patient consent

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There are no conflicts of interest.

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Newborns Presenting with Hyperthermia: Impact of Climate Change on Newborn Health

Hypothermia is an underlying cause of many neonatal deaths. Keeping babies warm is therefore considered critical for promoting the health, well-being, and survival of newborns. However, there is limited recognition of hyperthermia as a cause of neonatal morbidity and mortality. Rajasthan is well known for its hot weather. This year (May and June 2022) as in many other parts of India, Rajasthan reported a very hot summer with temperatures as high as 45°C–48°C. A study was conducted by the United Kingdom's Meteorological Office to assess the impact of climate change on the heat wave observed in India and Pakistan. One of the many salient conclusions was that human-caused climate change had increased the likelihood of the heat wave in Northwest India by hundred-folds.[1]

We run a network of primary healthcare clinics in South Rajasthan, called AMRIT Clinics. Each clinic serves a remote, rural, and tribal community of about 12000–15000 population, living in the hilly terrains of the Southern Aravalli range of Mewar. These regions are generally cooler than the desert districts of Jaisalmer, Barmer, and Jodhpur that fall in the region of Marwar. While most villages are electrified, the supply is erratic, and most households do not own electric fans. During this peak summer, we saw an alarming rise in the number of young infants presenting with hyperthermia.

We present two such newborns in this article, and through their clinical details and outcomes, aim at highlighting the challenges faced in the management of this frequently overlooked problem. We also frame a pathway through which global climate change affects the well-being and survival of newborns in the rural and tribal communities.

Case Studies

Case 1

On a hot afternoon in May, when the temperatures were around 45°C an old woman came to our clinic in panic about the condition of her 3-day-old grandson. Baby of Surya was a 3-day-old baby boy born at the AMRIT clinic at Manpur by a normal delivery. There were no risk factors for sepsis such as maternal fever, diarrhea, and leaking per vaginum. The baby, of second birth order, had cried immediately after birth, was kept for postnatal care for 48 h, and had been discharged once breastfeeding was initiated and both mother and baby deemed healthy by our team.

The following day, the family noticed that the baby did not appear well, felt hot to touch, had stopped breastfeeding, and was crying excessively. The family called up our clinic, and being aware of the rising cases of infant hyperthermia in nearby villages, our staff were immediately dispatched to make a home visit and evaluate the baby. They found the mother-son duo lying on a *khaat* (cot) in the verandah outside their mud house, with the baby wrapped in a thick woolen cloth, as per the customs of this region, i.e., newly delivered mothers are not kept inside the house.

Upon evaluation, the baby appeared irritable. His temperate was recorded as 103.6 °*F*, heart rate 146/min, respiratory rate 58/min, and there were no chest retractions. The remaining examination was normal, thus confirming the suspicions of hyperthermia. The team sat with the family and explained the reason for the baby's distress, while simultaneously removing the coverings and initiating sponging of the infant with tepid water. Within a short period of this intervention, the baby stopped crying and fell asleep [Figure 1]. We brought the baby and his mother to the clinic, where they were kept in a cool place. By the time, the baby awakened the temperature had dropped to 99.2 °*F*, the respiratory rate was 36/min, the heart rate 120/min and he started suckling well. The mother and baby were observed round the clock by our team. The next day when the baby was feeding well and afebrile, and the mother was reassured; we sent the baby home with a health worker and staff nurse who ensured that the family kept both mother and son indoors in a cooler place, and that the baby was not excessively clothed.

Case 2

Babies of Lalki were twin boys who had been born at term through cesarean section in a nearby hospital for being a primipara with twin pregnancy. There was no history of delayed cry in either. The first and second twins weighed 1.8 and 2 kg, respectively, at birth. The second twin had been discharged 48 h after birth. The first twin was kept in the neonatal intensive care unit (NICU) for Intrauterine Growth

Figure 1: Baby with hyperthermia in clinic

Retardation and poor feeding that was managed as presumptive sepsis and was discharged after a week. The AMRIT Clinic staff had conducted a postnatal check-up on the 8th day of life, when both babies were found to be healthy, were exclusively breastfed, and feeding well.

Coincidentally, just 2 days after managing the previous infant, our clinic staff got a call from one of our *Swasthya Kirans* (community health volunteers) who was concerned about the recent decrease in oral acceptance of the twins (who were now 16-day-old) and wanted us to make a home visit. When the team reached the house, they were surprised to see the babies lying in a bed [Figure 2] in a cowshed adjacent to their home, with a pedestal fan placed nearby. Although the mother was unhappy with this arrangement, she explained that it was nonetheless better than staying in their cemented house that had become unbearably hot.

The smaller baby was crying excessively and we were told that he had hardly breastfed since the morning. On examination, the baby appeared plethoric, had a temperature of 101.6°*F* and was dehydrated. At home, faced with the excessive heat and with urgency to manage the baby in the nonconducive environment, the team did not record the vitals, but ascertained that the babies were otherwise hemodynamically stable and there were no gross abnormalities in the examination. Making a diagnosis of environmental hyperthermia, we began sponging the baby until he became consolable and started breastfeeding. In order to keep the babies and mother cool, we showed the family how to drape saris around the cot, and keep them wet by sprinkling frequently with water [Figure 3]. We also instructed the mother to breastfeed frequently, change the babies' clothes to more breathable cotton, and sponge them whenever they felt excessively hot.

Discussion

Newborns do not sweat and their temperature regulating mechanisms are not fully developed. Hence, they are at high risk of developing hyperthermia when faced with high environmental temperatures or heat waves, as was seen in rural Mewar. Climate change is causing rise in environmental temperatures across the globe with associated implications on health. For example, there is scientific evidence of the ill effects of global warming on pregnancy outcomes. A meta-analysis of 14 studies concluded that for every 1° rise in environmental temperature, the risk of still births and premature births was rising by 5%.[2] However, there is limited documentation of the impact of environmental temperatures on neonatal survival and well-being, especially in the rural areas in India.

A study conducted in an Ahmedabad hospital in the harsh summer of 2010 reported a strong association between rising temperatures and NICU admissions of inborn newborns. Above the cut-off of 42°C, each increase of a degree of the daily maximum temperature was associated with a 43% increase in hyperthermia-related admissions. When exploring the possible reasons for this unusual phenomenon, it was noted that the maternity ward was on the top floor and thus became very hot. In the subsequent year, ward was shifted to the ground floor, following which there was a tangible reduction in NICU admissions due to hyperthermia.[3]

A review of climate change and its impact on newborn health in Africa cautioned that whatever gains were attained in improving newborn survival in the continent, would be reversed in the future due to the ill effects of climate change. The hypothesized pathways that linked climate change with newborn health included rising environmental temperatures and consequent hyperthermia, as well as droughts and consequent food insecurity.[4] This case report reveals how such a pathway is also playing out in rural and tribal hinterlands of India, where there are rising temperatures and high levels of food insecurity. We documented this in a study of child malnutrition in the select villages of this region: 56% of the families surveyed did not have any pulses and 26% did not have any cooking oil at home on the day of visit. Even those families did possess these items, had them in very small amounts. Very few households had any vegetables (14.4%), fruits (2.4%), and almost none had milk, eggs, or meat.[5]

Figure 2: Twin babies at home

Figure 3: Mother and babies cot draped with wet sheets

While global warming is probably the primary underlying reason for the unusually high ambient temperatures in this region, other attributable factors include deforestation and poor housing designs (i.e., cemented, poorly ventilated ill-planned houses). Since these regions have not faced such high temperatures historically, families have not been able to evolve ways or strategies of their own to help adapt to the high temperatures.

While the global warming needs to be tackled at international levels such as by reducing the consumption of nonessential goods, and reducing emissions of carbon dioxide and other greenhouse gases, there is also a strong felt need to improve the microclimate at the local level. Reforestation, growing trees, and using traditional designs and building material (i.e., wood and mud) would go a long way in reducing the ambient household temperatures. Furthermore, families and healthcare providers working in such areas need to be equipped with knowledge and skills to protect their newborns from high body temperatures like the simple but effective strategies that were employed in the management of both cases. Like hypothermia, health care workers, nurses, and pediatricians need to be sensitized to the manifestations, consequences, and management of hyperthermia in the Indian setting. In addition, for the sake of our newborn patients, we pediatricians as a community need to raise our voices against climate change, deforestation, and unbridled urbanization.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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A Child with Recurrent Respiratory Infections: When Right is Not Always Right!

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Clinical Description

A 12-year-old girl presented with a history of recurrent episodes of fever, dry cough, and nasal discharge, starting from early infancy. Each episode lasted for 3–5 days and responded to a combination of antibiotics, cough syrups, and bronchodilators, prescribed by local practitioners. The cough gradually increased in severity and became productive by 8 years of age. Subsequently, the child also started experiencing recurrent episodes of a feeling of tightness in the chest, wheezing, and difficulty in breathing, which were triggered by upper respiratory tract infections. These episodes occurred 3–4 times a year. There was no exacerbation with physical exertion, cold air, exposure to dust or smoke, or seasonal variation. She was treated with short courses of bronchodilators and oral steroids on some occasions.

During her most recent episode, she was hospitalized elsewhere for 7 days. There, she was presumed to have an acute episode of bronchial asthma, complicated by pneumonia, hence was prescribed inhaled corticosteroids, intravenous (IV) antibiotics, and supplemental oxygen. A chest radiograph was done at that hospital [Figure 1a]. She was referred to our institution due to the persistence of symptoms despite these interventions, and to ascertain the diagnosis.

The child was second in birth order, born at term by vaginal delivery (at home). There was no history of parental consanguinity. Her older and younger siblings (aged 16 and 9 years, respectively) were healthy. There was no history of tuberculosis or similar illness in any family member. The child had attained age-appropriate developmental milestones and was studying in class six. Her vaccination was up to date.

What additional history can help to determine the diagnosis?

The clinical phenotype suggested recurrent respiratory tract infections that were initially mild but progressively increased in severity. There was no history of delayed passage of meconium at birth, prolonged neonatal jaundice, the passage of greasy or bulky stools, recurrent episodes of ear discharge, recurrent diarrhea or skin pustules, lymph node enlargement, episodes of syncope or chest pain, or bluish discoloration of nails or lips. There was no history of witnessed or suspected foreign body aspiration, recurrent feed aspiration, choking episodes while eating or drinking, or history of blood transfusion. There was also no history of close contact with tuberculosis. These points in history ruled out cystic fibrosis, primary/secondary immune deficiency, congenital cardiac disease, aspiration syndromes, and a forgotten airway foreign body.

At presentation, the pulse rate was 89/min, respiratory rate 26/min, blood pressure 112/65 mmHg (all within the normal range), temperature 99°F, and oxygen saturation 97% in room air. The weight was 29 kg (−1.6 z-score), height was 137 cm (−1.7 z-score), and body mass index was 15.45 (−0.98 z-score). There was mild pallor, but no clubbing, lymphadenopathy, elevated jugular venous pressure, icterus, or signs of nutritional deficiency. The tonsils were not enlarged. Tenderness was evident over both maxillary sinuses, but not the frontal or ethmoidal sinuses. The nose and ear examinations were normal. A Bacille Calmette–Guérin scar was noted.

The respiratory system examination showed a centrally positioned trachea, symmetric chest wall shape and movements, equal breath sounds, and bilateral, diffuse, end-expiratory wheeze. There were no crackles. The heart sounds were normal but more prominent on the right side of the chest. There was no murmur. On abdominal percussion, liver dullness appeared to be present on the left side. Neurological system examination was normal.

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What diagnoses would you consider at this stage and why?

The child had recurrent respiratory infections from early infancy, progressing to develop the aforementioned manifestations, indicative of chronic suppurative lung disease (CSLD) by the age of 8 years. She also appeared to have had recurrent sinusitis, although there was no otitis media. Therefore, the differential diagnoses could be primary ciliary dyskinesia (PCD), or congenital airway malformations. Other clinical possibilities had already been excluded by elicitation of a detailed history. The presence of wheezing against the background of CSLD was attributed to secondary allergic bronchopulmonary aspergillosis (ABPA), complicating the primary diagnosis.

What are the salient features in the chest X-ray?

The initial chest X-ray that had been done outside [Figure 1a] had poor penetration, evidenced by the absence of discernible intervertebral spaces. The lung parenchyma appeared normal, although careful examination raised the suspicion of dilated bronchi. There was a single calcified right axillary lymph node. As the quality of this X-ray was not optimal, we repeated one in our institution [Figure 1b]. This showed dextrocardia with the cardiac apex oriented toward the right side, and multiple dilated bronchi suggesting bronchiectasis. The calcified lymph node was also evident but on the left side. We concluded that the marker on the first chest X-ray had been placed incorrectly; whereby dextrocardia was missed altogether. Further, the poor exposure resulted in difficulty to appreciate bronchiectasis.

What should be the next steps of evaluation?

Formal otorhinolaryngological examination confirmed frontal sinusitis, bilateral intact tympanic membranes, and no middle-ear effusion. An X-ray of the paranasal sinuses showed bilateral opacified maxillary sinuses but unremarkable bilateral ethmoidal, frontal, and sphenoid sinuses. Pure-tone audiometry and impedance tympanogram confirmed normal hearing.

The presence of dextrocardia prompted us to perform ultrasonography of the abdomen which showed the liver on the left side and the spleen on the right side, confirming abdominal situs inversus. There was also a right-sided aortic arch.

We investigated for secondary infections. Sputum examination did not show any bacteria on Gram staining. However, the culture yielded *Pseudomonas aeruginosa*. Sputum smear microscopy showed pseudohyphae but no fungi on culture.

To confirm bronchiectasis radiologically while avoiding the excessive radiation of a computed tomography scan, chest magnetic resonance imaging was performed [Figure 2]. This confirmed the right-sided aortic arch, dextrocardia, and situs inversus. There was bilateral central bronchiectasis with otherwise unremarkable lung parenchyma. Thus, the clinical diagnosis considered was CSLD with sinusitis, due to a possible PCD with situs inversus, most likely Kartagener's syndrome. Wheezing was attributed to secondary ABPA.

What to do next to confirm the diagnosis?

To confirm PCD, nasal mucosal scrapings from the right inferior turbinate were sent for ultrastructural examination of cilia by transmission electron microscopy (TEM). However, the quantity of samples sent was reported as inadequate. Hence, a flexible fiberoptic bronchoscopy-guided tracheal/bronchial mucosal biopsy sample for TEM examination was planned during the follow-up.

Investigations for ABPA showed serum total immunoglobulin E (IgE) elevated to 1171 IU/ml, (normal <100 IU/ml), however, *Aspergillus* specific IgE was 0.10 kUA/l (laboratory normal <0.35 kUA/l), and *Aspergillus* specific IgG was 1.08 U/ml (laboratory normal <8.0 U/ml). The absolute eosinophil count was also normal –68 cells/μ*L* (0.5%), hence, ABPA could not be confirmed. Skin prick test for *Aspergillus* antigen was unavailable in our institution.

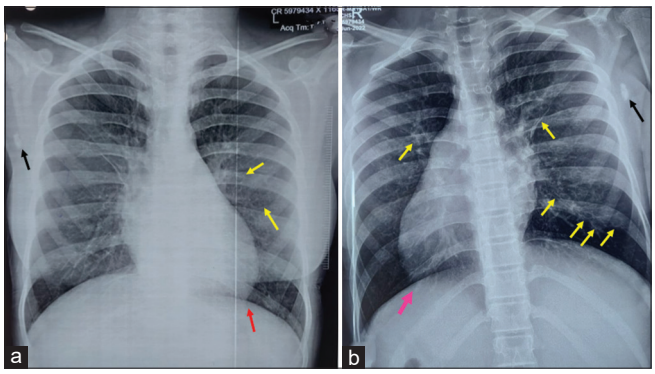

Figure 1: (a) Chest X-ray (with incorrect marker) suggesting left-sided heart and cardiac apex (red arrow), suspicion of bronchiectasis (yellow arrows), and a calcified axillary lymph node on the right side (black arrow). (b) Chest X-ray showed dextrocardia with right-sided cardiac apex (pink arrow), bilateral bronchiectasis (yellow arrows), and a calcified axillary lymph node on the left side (black arrow).

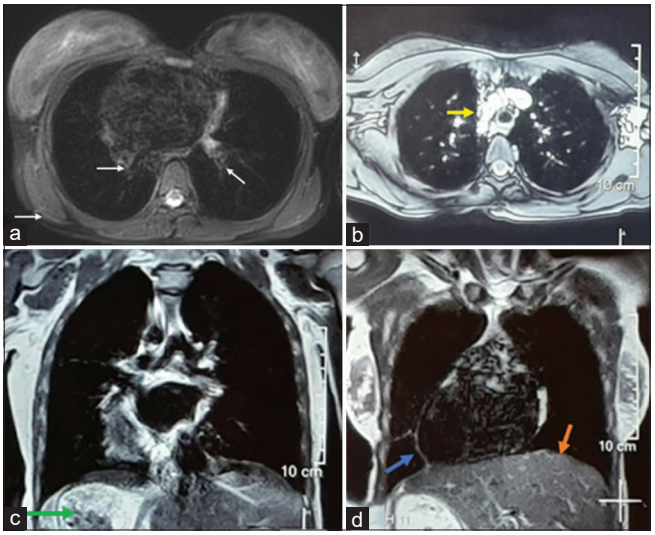

Figure 2: Axial T2-weighted MRI (a and b) lung section showing mild bilateral central bronchiectasis (white arrow), right-sided aortic arch (yellow arrow). Coronal T2-weighted MRI (c and d) lung cuts showing dextrocardia (blue arrow), liver on the left side (orange arrow), spleen (red arrow), and stomach (green arrow) on the left side.

Management

The child received IV antibiotics for 7 days as per the sputum culture sensitivity pattern. Her family was taught gentle chest physiotherapy and airway toileting. As ABPA had been suspected, she was administered oral corticosteroids, which were given for only 5 days as it was not confirmed. She also received inhaled bronchodilator for 5 days. The otorhinolaryngologist prescribed nasal corticosteroids for 3 months, for chronic sinusitis. The child improved with these medications.

Discussion

PCD is a rare, but clinically and genetically, nonhomogeneous group of disorders of ciliary motility. It is inherited in an autosomal recessive manner. Its estimated prevalence is about one in 10,000–40,000 in Norwegian and Japanese population surveys of situs inversus and bronchiectasis.[1]

Cilia are present at the apical surface of the epithelial cells of the upper and lower respiratory tracts, female reproductive tract, spermatozoa, and ependymal lining of brain ventricles.[2] Abnormal ciliary function in the respiratory tracts impedes clearance of airway secretions, resulting in increased susceptibility to recurrent bacterial infection, ultimately leading to the development of bronchiectasis.[1] During embryogenesis, motile cilia play a pivotal role in determining organ laterality, hence, laterality defects are observed in half the cases of PCD.[1] Kartagener's syndrome is a variant of PCD, with the classic triad of sinusitis, bronchiectasis, and situs inversus.[3]

Clinical symptoms and signs of PCD include respiratory distress at birth in term neonates, early and recurrent rhinitis, persistent serous otitis media, chronic wet cough, and sometimes hydrocephalus.[1] The diagnosis of PCD is often delayed due to a low index of suspicion. However, it is one of the rare causes of chronic lung disease, presenting with respiratory distress starting from birth.

A diagnostic predictive score, the PCD rule (abbreviated as PICADR) is helpful in suspecting PCD and considering further evaluation to confirm the diagnosis of PCD. It is a simple, seven-point questionnaire, to be applied to children with chronic respiratory symptoms, originating in early infancy/childhood. Four points are scored for the presence of situs abnormality, two points each for being born at tern, experiencing respiratory symptoms from the neonatal period, admission to a neonatal unit, and the presence of a congenital heart defect. One point each is scored for the presence of persistent perenniel rhinitis and the presence of chronic ear symptoms. Thus, out of a total possible score of 14, the index child scored 10. A score >5 has sensitivity and specificity of 0.90 and 0.75, respectively.[4]

Currently, nasal nitric oxide measurement is the preferred screening test for suspected PCD.[5] Assessing ciliary beat pattern and ciliary beat function using high-speed video microscopy[6] is also helpful, although it cannot differentiate genetic PCD from secondary ciliary dyskinesia caused by bacterial or viral infections.[5] However, these facilities are unavailable in our institution. In India, they are available at AIIMS, New Delhi, although other institutions (including ours) are attempting to establish similar services. TEM ciliary ultrastructural examination was earlier considered the gold standard test. The classic defects are the absence of outer dynein arms, combined absence of outer and inner dynein arms, and microtubular disarrangement with the absence of inner dynein arms.[7] However, it can be normal in about 20% of PCD cases. Genetic confirmation of PCD is still evolving. To date, mutations of only 60% of PCD cases have been identified.[1] Immunofluorescence-linked antibodies to ciliary proteins can identify their absence or mislocalization and can be used to diagnose PCD. However, currently, there is no single gold standard investigation for diagnosing PCD.

PCD can result in long-term lung damage, but it has a relatively better prognosis than cystic fibrosis. In later life, male infertility may be observed. The outcome of PCD depends on genetic and phenotypic heterogeneity, associated comorbidities, and access to appropriate care. However, some children progress to severe bronchiectasis, end-stage lung disease, and premature death.[8]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Gippi

"Gippi" is a Hindi movie directed by Sonam Nair and released in 2013. It showcases the journey of the 14-year-old protagonist (of the same name) as she navigates the stormy waters of adolescence. Genes and junk food have combined to distort Gippi's body image. The mirror and a forever judgmental society shame her with colloquial adjectives. The initial part of the film shows her swinging between despair and indifference, never really knowing which path to take, and appearing to exist without any tangible direction. Yet the depiction of her ear for music, flair for dancing, and unreserved enactment of her idol Shammi Kapoor give the viewers a glimpse of her hidden persona – that of a happy-go-lucky, fun-loving, and carefree girl.

Society's metamorphosis in family structure and dynamics places fresh challenges for teens. Gippi's mother and brother are steadfast confidantes, but the bond with her father is long distance and complicated, as he is forging a new relationship of his own. Gippi and her brother are not uncivil toward their father. Yet they empathize with their mother and clearly visualize her pain. Adolescent resilience is demonstrated when the siblings attend their father's engagement and marriage, but refuse to participate in the "new" family photograph till their mother is included as well.

A trip to the engagement party contrives to set Gippi up with a handsome hunk, and Arjun and her adolescent romantic instincts get awakened for the first time. The initial chance encounters and subsequent more purposeful attempts by Gippi to meet the young man are inadvertently aimed at social redemption, especially in front of her bête noire, Shamira. Gippi's dalliance with Arjun meets an ignominious end, ironically in front of her arch rival Shamira, sending her headlong into the depths of despair. Fortunately, family and friends stand rock solid behind her as her bruised heart recovers and she regains her bearings.

While Shamira has beauty and brains, she is far too condescending and proud. Gippi possesses neither academic nor sporting abilities, is plagued by body image issues, and yet endears herself to the viewers by simply being human and vulnerable. Such a chalk-and-cheese story is always destined for confrontation, and that materializes in the form of the election of the head girl. Gippi picks up the gauntlet thrown by her frenemy. The didactic cinematic script inevitably picks Gippi as the winner and emphasizes the importance of loving ourselves as we are. Later, Gippi's renunciation of the head girl's medal to Shamira displays melodramatic magnanimity and an attempt to seek divinity in forgiveness.

The script and screenplay appear dictated by cinematic viability, and yet the characterizations do leave an impression of authenticity. The effort to be totally and morally correct by the director does take a bit of the sheen away from reality, but nonetheless, the intent is admirable. Overall, the film is a delightful insight into adolescence with its multifarious vulnerabilities, challenges, and responsibilities.

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There are no conflicts of interest.

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Feeding Your Child – Parental Perceptions and Pediatrician's Problems

"If music be the food of love, play on." Indian parents may or may not know their Shakespeare, but they certainly believe in a closely drawn parallel (with due apologies to the great bard), "*If food be the proof of love, feed on."* Indian culture is well known for treating guests as God and offering them the best of food. When one can do this for guests who stay with us merely for a few days, why would parents not want to feed (or overfeed) their beloved young ones as proof of their underlying love?

As a pediatrician, I have had several "encounters" with parents who are worried about the food habits of their healthy-looking toddlers. You frequently hear about how the child was doing well till 6–9 months of age, stopped eating, and has now (according to them) become woefully thin. "Doctor, all my relatives ask me why I am not feeding my child?" is the mother's usual grievance and you respond with your usual platitudes of reassurance. The grandmother will balefully glare at, and blame the hapless mother with a snarky, "She spends an hour to feed her child, and he eats only a few mouthfuls." These complaints are followed by contradictory statements by the worried mother (and nowadays, equally anxious father), "He hardly eats anything, but is so active that he wears me out. I don't know where he gets his energy from." I proceed to tell them that their child is healthy, they shouldn't worry as he is growing well, and it is they who require extra energy. I know they don't believe me!

Then, you have parents who continue to "feed on" their overtly obese children despite your repeated caution and instruction, "Please cut down on junk food, sugar, and deep fried snacks." "Oh Doctor, my child hardly eats anything," is the standard reply. You wonder at their blatant disregard for the laws of science, and how their child can create such a lot of matter from nothing at all. "Okay, you must encourage him to play and be active every day" – you say. "He wants me to play with him, but I just don't have the time!" laments the fond parent or "You tell him, doctor - he doesn't listen to me, and will not stop watching TV!"

Another common remonstrance heard when you diagnose a child with an upper respiratory tract infection is "I told her not to eat ice cream/sweets/banana, but did she listen?" Again you wonder, with so much information circulating regarding airborne/droplet infections following the pandemic, why do parents still associate food with coughs and colds? One often hears about foods that are "hot," foods that are "cold" and foods that can do all sorts of magic. And now with easy access to Dr. Google, you also hear about exotic food previously available only in the West or the extremely rich. "Doctor, my daughter is so constipated. Do you think prunes soaked in hot water will help her?" or "Doctor my son refuses to eat broccoli or flax seeds. Can you prescribe something to make him eat those?" or the most frequent plea, "I need you to write a 'good' tonic that will make my child eat!"

However easy as it is to poke fun at caregivers, one must not forget that it is their love and concern for the child that is their driving force. We are all familiar with a bygone era of joint families where multiple siblings ate, got schooled, and grew up without any bother. Today, most nuclear families have a single child or two. And each child has two devoted parents who only want the best for them. We, as pediatricians must show them that when it comes to unhealthy food or eating habits, "more is not merrier," "bigger is not better," and "strength does not lie in numbers."

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