Paediatric acute respiratory distress syndrome and haemophagocytic lymphohistiocytosis complications of scrub typhus: a case report

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In June 2020, a previously healthy 7-year-old boy presented with a 1-week history of persistent fever. He had an unremarkable medical history, and had gone hiking a week before the onset of his fever. He was initially treated for a presumed viral illness but his condition worsened over the subsequent 2 days. His fever became high and fluctuating, with a peak of 39°C, and he developed dyspnoea without cough. He had no headache or body aches. Physical examination revealed crepitations with diminished breath sounds over both lung fields and tachypnoea with a respiratory rate of 30 per minute. Cervical lymphadenopathy and hepatomegaly were present. There was no eschar. He had distributive shock with hypotension (80/40 mm Hg) and tachycardia (150 beats per minute) and a norepinephrine infusion was commenced. Within one day, type I respiratory failure became evident with increasing oxygen requirement from room air to FiO_2 0.4 and continuous positive airway pressure of 6 cmH_2O to maintain oxygen saturation above 90%. The PaO_2:FiO_2 ratio was 232.5 mm Hg. Plain radiograph of the chest revealed bilateral opacities and peribronchial thickening (Fig). Echocardiography and lung ultrasound confirmed normal heart function and the absence of pleural effusion. By definition, the boy was diagnosed with paediatric acute respiratory distress syndrome (PARDS: an acute lung injury occurring within 7 days of a known clinical insult, with acute hypoxaemia of PaO_2:FiO_2 ratio ≤300 when the child is on non-invasive ventilation, and new infiltrates consistent with acute pulmonary parenchymal disease on chest radiograph, which cannot be explained by acute left ventricular heart failure or fluid overload), where he had progressive respiratory failure and bilateral diffuse infiltration on chest radiography.[1] Further blood tests and bone marrow findings met the diagnostic criteria for haemophagocytic lymphohistiocytosis (HLH: a life-threatening clinical syndrome of systemic hyperinflammation and progressive immune-mediated organ damage due to excessive immune activation): anaemia (haemoglobin 8.3 g/dL), thrombocytopenia (45×10^9/L), hypertriglyceridaemia (4.5 mmol/L), high ferritin (4467 pmol/L), hypofibrinogenaemia (0.9 g/L), and elevated soluble CD25 (8569 pg/mL).[2] Bone marrow aspiration and trephine biopsy showed haemophagocytosis. There was no evidence of Epstein–Barr virus association on immunohistochemical analysis. *Orientia tsutsugamushi* antibody titre of 512 increased to 4096 (ie, more than a fourfold increase) after 2 weeks. The child was diagnosed with PARDS and secondary HLH associated with scrub typhus infection and

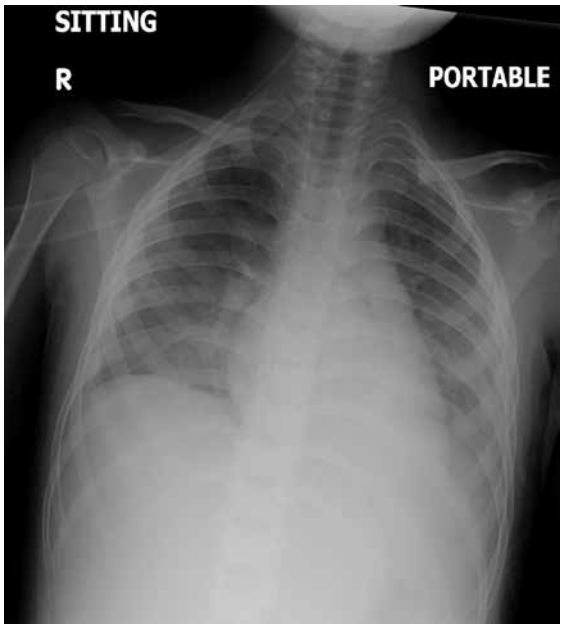

FIG. Plain radiograph of the chest of a 7-year-old boy presenting with paediatric acute respiratory distress syndrome and haemophagocytic lymphohistiocytosis following hiking. Peribronchial thickening at bilateral perihilar and right paracardiac regions, and atelectasis at right lower, left middle and lower zones

prescribed oral doxycycline 50 mg twice daily (~3.7 mg/kg/day) for the scrub typhus. Intravenous dexamethasone 5 g every 12 hours (10 mg/m^2/day) was commenced as treatment of HLH with a starting dose as per the HLH-2004 study protocol. He became afebrile within 1 day of commencing treatment and respiratory distress gradually resolved. He was weaned off continuous positive airway pressure ventilation after 3 days. Platelet count rose to >100 × 10^9/L after 4 days. Ferritin lowered the day after treatment and was within normal range after 2 weeks. The boy completed a 1-week course of doxycycline and dexamethasone was also tapered off in 1 week.

Discussion

Our patient presented with non-specific symptoms of scrub typhus and developed severe complications including PARDS and HLH without the pathognomonic eschar. Scrub typhus is caused by the bacterium *O tsutsugamushi* and is spread to humans through the bites of infected chiggers, *Leptotrombidium* mites, that can be both a vector and a reservoir for *O tsutsugamushi*.[3] It is a notifiable disease in Hong Kong with between 7 and 28 cases reported each year over the past 10 years.[4] Symptoms of scrub typhus usually begin within 10 days of being bitten and can range from non-specific signs including fever, headache, body aches and rash, to multiorgan failure and death with a median mortality rate of 6% if left untreated.[3] Although eschar is pathognomonic for scrub typhus, it is rare among Southeast Asian patients. Laboratory confirmation of the diagnosis usually requires indirect fluorescent antibody test and is the mainstay of serologic diagnosis. Polymerase chain reaction assay of whole blood sample if available can speed the diagnosis.

Acute respiratory distress syndrome is a serious complication of scrub typhus; it has been reported in 4% to 22% of cases,[5,6] and can involve over 50% of children who developed secondary HLH associated with scrub typhus infection.[7] The pulmonary manifestations vary from bronchitis and interstitial pneumonitis to acute respiratory distress.[5,6] Acute respiratory distress has also manifested in many patients with HLH due to other causes and has been reported as the initial manifestation of HLH. Nahum et al[8] reported that 7 of 11 children with HLH and multiple organ failure exhibited PARDS after HLH was diagnosed, highlighting the importance of close monitoring and early intervention for children with PARDS and HLH. The presentation of acute respiratory distress syndrome in children differs from that in adults and a consensus on a formal PARDS definition was reached in 2015 by the Paediatric Acute Lung Injury Consensus Conference.[1]

In some cases, HLH can cause cytokine release syndrome, a life-threatening disorder of severe excessive inflammation (hyperinflammation) caused by uncontrolled proliferation of activated lymphocytes, macrophages and secretion of inflammatory cytokines.[9] Although rare, *O tsutsugamushi* is a significant cause of HLH, especially in Asia.[7] The HLH-2004 protocol, which includes etoposide, dexamethasone and cyclosporine as the initial therapy, is designed for treatment of patients with primary HLH.[2] For patients with secondary HLH, treatment of the underlying infection or malignancy may help control the HLH and avoid the need for cyclosporine and etoposide. Single antibiotic therapy with doxycycline, minocycline, chloramphenicol, azithromycin or clarithromycin has been reported to result in rapid defervescence in patients with HLH associated with scrub typhus.[10] Thus, an accurate diagnosis of scrub typhus in patients with HLH can help timely targeted antibiotic therapy with subsequent rapid clinical improvement.

This case illustrates an atypical severe manifestation of scrub typhus presenting with non-specific signs and symptoms resulting in complications including PARDS and HLH. Early diagnosis and treatment with doxycycline are crucial to prevent complications. Physicians should be vigilant for scrub typhus as a potential diagnosis in a child who presents with pyrexia of unknown origin and a history of participation in rural outdoor activities.

Author contributions

Concept or design: RCM Fung, KKY Leung, CC Au, KL Hon.
Acquisition of data: RCM Fung, KL Hon.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: RCM Fung, KKY Leung, KL Hon.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, KL Hon was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

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Ethics approval

The patient was treated in accordance with the tenets of the Declaration of Helsinki. The patient's parents provided written informed consent for all treatments and procedures and consent for publication.

References

1. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med 2015;16:428-39.
2. Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-31.
3. Peesapati N, Rohit T, Sunitha S, Pv S. Clinical manifestations and complications of scrub typhus: a hospital-based study from North Andhra. J Assoc Physicians India 2019;67:22-4.
4. Center for Health Protection, Department of Health, Hong Kong SAR Government. Number of notifiable infectious diseases by month. 2020. Available from: https://www.chp.gov.hk/en/statistics/data/10/26/43/6896.html. Accessed 25 Jun 2020.
5. Sankuratri S, Kalagara P, Samala KB, Veledandi PK, Atiketi SB. Scrub typhus with acute respiratory distress syndrome (ARDS) and its management in intensive care unit: a case report. J Clin Diagn Res 2015;9:OD10-1.
6. Kumar Bhat N, Dhar M, Mittal G, et al. Scrub typhus in children at a tertiary hospital in north India: clinical profile and complications. Iran J Pediatr 2014;24:387-92.
7. Naoi T, Morita M, Kawakami T, Fujimoto S. Hemophagocytic lymphohistiocytosis associated with scrub typhus: Systematic review and comparison between pediatric and adult cases. Trop Med Infect Dis 2018;3:19.
8. Nahum E, Ben-Ari J, Stain J, Schonfeld T. Hemophagocytic lymphohistiocytic syndrome: Unrecognized cause of multiple organ failure. Pediatr Crit Care Med 2000;1:51-4.
9. Hon KL, Leung KK, Oberender F, Leung AK. Paediatrics: how to manage septic shock. Drugs Context 2021;10:2021-1-5.
10. Hon KL, Leung AS, Cheung KL, et al. Typical or atypical pneumonia and severe acute respiratory symptoms in PICU. Clin Respir J 2015;9:366-71.