Haemophagocytic lymphohistiocytosis with pulmonary mucormycosis: fatal association

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DESCRIPTION

We report a 7-month-old infant, who presented with acute febrile encephalopathy, and was in respiratory failure at admission, for which he was started on invasive ventilation. Systemic examination was unremarkable. Investigations revealed pancytopenia (haemoglobin—82 g/L; total leucocyte count— 2.4×10^9 /L; platelet— 49×10^9 /L), coagulopathy (International normalized ratio—2.00, Partial Thromboplastin Time—48 s), transaminitis (aspartate transaminase—708 IU/L, alanine transaminase—1553 IU/L) with normal bilirubin. Procalcitonin was elevated and he was started on doxycycline, ceftriaxone and acyclovir. Neuroimaging was normal. Blood culture was sterile and serologies for scrub typhus, leptospirosis, dengue and hepatitis A–E were negative. Ferritin was elevated and fibrinogen was low. Cerebrospinal fluid (CSF) study showed lymphocytic pleocytosis (80 cells/ μ L, 100% lymphocytes) with elevated protein (378 mg/dL) and normal sugar (110 mg/dL) with negative Gram stain and sterile culture. PCR for herpes simplex virus (types 1 and 2) was negative.

He developed progressive multiorgan dysfunction, in the form of acute respiratory distress syndrome, acute kidney injury and shock, to which he succumbed on D3 of hospital stay.

Postmortem biopsies from lung showed alveolar spaces filled with neutrophil-rich infiltrate with broad aseptate hyphae conforming to morphology of mucormycosis (figure 1A), and bone marrow showed increased histiocytes showing florid haemophagocytosis (figure 1B).

Our index child had features of multiorgan dysfunction, with pancytopenia, hyperferritinaemia and hypofibrinogenaemia, although the diagnosis of haemophagocytic lymphohistiocytosis (HLH) could only be made postmortem using the HLH 2004 criteria.^{1 2} Liver dysfunction has been well described in HLH, and usually presents as elevated transaminase levels with jaundice seen in less than half the cases.³ Central nervous system is quite often involved with neurological symptoms in as many as 46%, and CSF pleocytosis may occur in 56% of cases.⁴

Distinguishing HLH from bacterial sepsis is extremely difficult since they may have coexisting features like pancytopenia, coagulopathy and multi-organ dysfunction. Procalcitonin which is used as a marker for sepsis can also be elevated in HLH.

Mucormycosis is the third most common fungal infection in children, with *Rhizopus* being the most frequently isolated species. Predominant risk factors include haematological malignancy, stem cell or solid organ transplant recipients, diabetes mellitus, iron overload and immunocompromised states.⁵ However, there may not be any evident risk factor as in our index child.⁶

Mucormycosis-associated HLH has rarely been described in literature, and has only been reported in adults.

There have been infrequent reports of mucormycosis-associated HLH in adults by Inagaki *et al.*,⁷ Rajagopala *et al.*⁸ and Arena *et al.*⁹ However, all were associated with 100% mortality rate, and diagnoses could be established by postmortem biopsies only.

Figure 1 (A) Chest X-ray showing bilateral homogenous fluffy infiltrates. (B) Photomicrograph of the postmortem lung biopsy showing alveoli filled with neutrophil-rich exudates along with many fungal profiles. In the inset photograph, these are seen as well-defined hyphae and irregular-shaped-foldable profiles which are highlighted by the black arrows (H&E, $\times 150$, inset— $\times 500$).

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Management of HLH is based on aetiology. Primary HLH is treated as per HLH-2004 protocol, which includes vincristine, etoposide, cyclosporine A and dexamethasone. Haematopoietic stem cell transplant is indicated in proven familial or genetic disease, or that which is severe and persistent, or reactivated. In case of infection-triggered HLH, adequate treatment of the triggering infection is necessary. Emapalumab, a monoclonal antibody against interferon γ , has been recently approved by Food & Drug Administration (FDA) for primary HLH.

Learning points

- ▶ Haemophagocytic lymphohistiocytosis (HLH) is a strong mimicker of severe sepsis with multiorgan dysfunction.
- ▶ Pancytopenia, low fibrinogen and elevated ferritin can help in early identification.
- ▶ Mucormycosis-associated HLH is extremely rare and invariably fatal as per literature.

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