

Hyperleucocytosis as an unusual presentation of hypereosinophilic pneumonitis with acute respiratory distress syndrome

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Abstract

Idiopathic hypereosinophilic syndrome in children is a rare disease. Even with improved understanding of eosinophilic disorders and recent advances in diagnostic modalities, evaluation of hypereosinophilia remains challenging due to heterogeneous etiologic factors. In acute clinical settings, the management plan is often unclear as the condition is not encountered frequently. It is often associated with leucocytosis, but hyperleucocytosis causing multiorgan dysfunction in the absence of malignancy is rarely seen. A previously well 5-year-old boy presented to our emergency room with a 2-week history of fever, progressive cough and dyspnoea, rapidly progressing to respiratory failure and acute respiratory distress syndrome. Hyperleucocytosis with hypereosinophilia on peripheral blood film, bilateral pulmonary infiltrates on X-ray and ground glass opacities suggested hypereosinophilic syndrome with secondary acute respiratory distress syndrome. Owing to severe and rapidly increasing leucocytosis, malignancy was highly suspected, but it was ruled out along with secondary hypereosinophilic syndrome after extensive investigations, and acute respiratory distress syndrome in this child was attributed to Idiopathic Hypereosinophilic Syndrome. Eosinophilia had a dramatic response to high dose corticosteroid therapy. To conclude, in patients with hypereosinophilic syndrome, possibility of progression to acute respiratory distress syndrome should be anticipated and managed accordingly.

Keywords

Hypereosinophilia, idiopathic hypereosinophilic syndrome, hyperleucocytosis, leucocytosis, leucopheresis, respiratory failure, ARDS, corticosteroid therapy, methylprednisolone pulse therapy

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Introduction

Eosinophilia is defined as an increase in the number of eosinophils (EOs) in the blood, observed in absolute eosinophil counts (AEC) above 500 cells/mm³, which can further be classified as mild (AEC 500–1500 cells/mm³), moderate (AEC 1500–5000 cells/mm³), or severe (AEC above 5000 cells/mm³). The term hypereosinophilia (HE) is used when patient has moderate to severe persistent blood eosinophilia, defined as a blood AEC above 1500 cells/mm³ obtained on at least two separate occasions (interval more than 1 month) or marked tissue eosinophilia, and it is termed hypereosinophilic syndrome (HES) when HE is associated with end organ damage.

HE can be classified as primary, secondary or idiopathic:

- Primary – clonal proliferation or malignancy;
- Secondary – reactive response to infectious, allergic or vasculitic causes;
- Idiopathic HE.

HES is a rare entity in children, and the exact incidence is uncertain due to paucity of data in paediatric patients.^{1,2} It is often associated with leucocytosis, and it may have a varied clinical presentation, mainly with dermatologic, pulmonary

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and gastrointestinal manifestations. It is crucial to look for associated organ dysfunction in these patients.³ HES is not considered a usual cause of respiratory failure or acute respiratory distress syndrome (ARDS) in children.

In this article, we report an unusual case of HE with ARDS and neurological involvement who showed a dramatic response to management of hyperleucocytosis with HE. Extensive investigations ruled out malignancy and primary and secondary HE, hence managed as idiopathic hypereosinophilic syndrome (IHES).

Case presentation

A previously healthy 5-year-old boy presented with a 2-week history of fever, cough and shortness of breath. On examination, he was tachypneic, hypoxic and had bilateral diffuse wheeze and crepitations. Past history was significant only for infrequent visits to the emergency room (ER) with complaints of shortness of breath which had responded to nebulisation with albuterol. There was no family history of asthma or atopy. The child was not on any regular medication.

Investigations

Preliminary investigations revealed unusually high leucocytosis. White Blood Cell (WBC) count was 194,000 cells/mm³ (50% EOs), and it rose further to 224,000 cells/mm³ within 24 h. There was also associated anaemia and thrombocytopenia. Peripheral blood smear was suggestive of eosinophilia with reactive lymphocytes, without evidence of blast cells. Lactate dehydrogenase (LDH) was elevated at 785 U/L.

As seen in Figure 1, the chest X-ray demonstrated features of early ARDS. The bilateral diffuse alveolar opacities progressed rapidly to white out lungs. Cardiac function was good on echocardiography. Urgent leucopheresis was done for the extreme hyperleucocytosis.

The patient's respiratory status progressively worsened, requiring mechanical ventilation, but as seen in Figure 2, there was significant improvement in lung infiltrates after leucopheresis, and the patient could be subsequently extubated 1 week later. Chest computed tomography (CT) scan (Figure 3) revealed bilateral ground glass opacities. CT scan of para nasal sinuses was normal. On assessment of the patient post extubation, neurological involvement was apparent in the form of hyperreflexia, asymmetrical quadriparesis, spasticity and encephalopathy. As evident in Figures 4 and 5, Magnetic Resonance Imaging (MRI) of the brain showed multiple confluent white matter lesions of bilateral semiovale with post-gadolinium enhancement suggesting multiple microhaemorrhages and restricted ischemic insult, raising the suspicion of vasculitis.

Differential diagnosis

Bone marrow (BM) biopsy showed markedly hypercellular marrow with increased erythroid precursors, but no blast

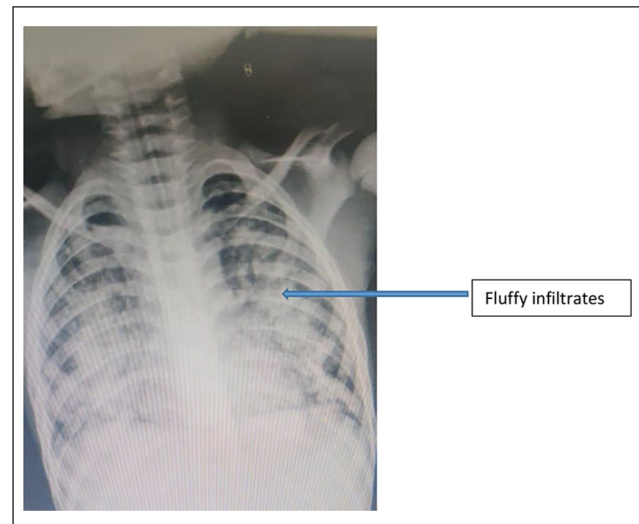


Figure 1. Chest X-ray post admission: extensive bilateral pulmonary infiltrates and alveolar shadowing suggestive of ARDS. ARDS: acute respiratory distress syndrome.

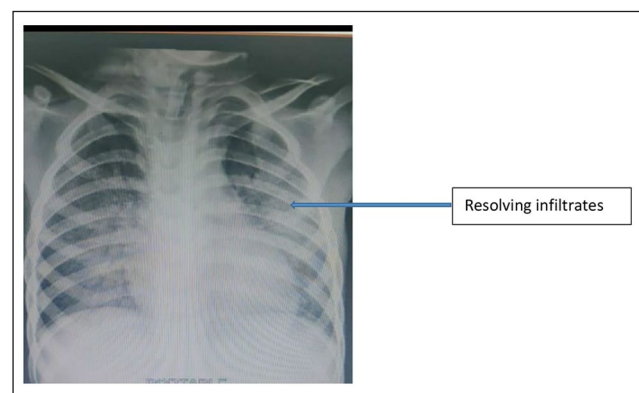


Figure 2. Chest X-ray post extubation: resolving pulmonary infiltrates.

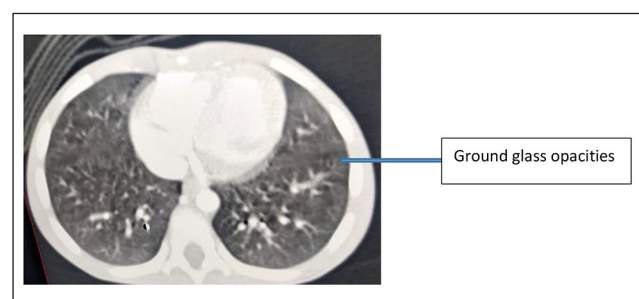


Figure 3. Chest CT scan: bilateral diffuse ground glass opacity signifying ARDS. CT: computed tomography; ARDS: acute respiratory distress syndrome.

cells or hemophagocytes were seen, and flow cytometry was normal. Cytometric studies for FIP1L1/PDGFR mutation, ABL/BCR and PDGFRB were negative. Immunophenotyping of lymphocytes was normal.

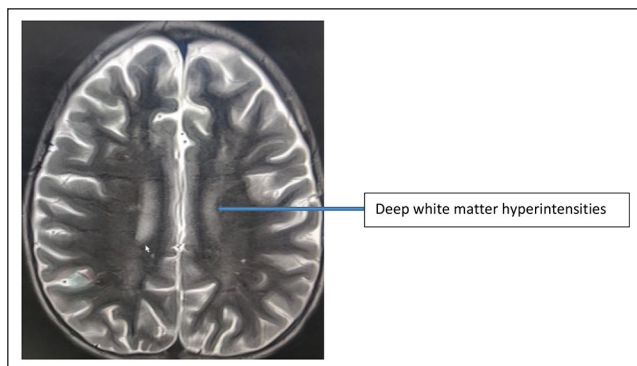


Figure 4. MRI of the brain: multiple enhancing confluent white matter lesions of bilateral semiovale. MRI: magnetic resonance imaging.

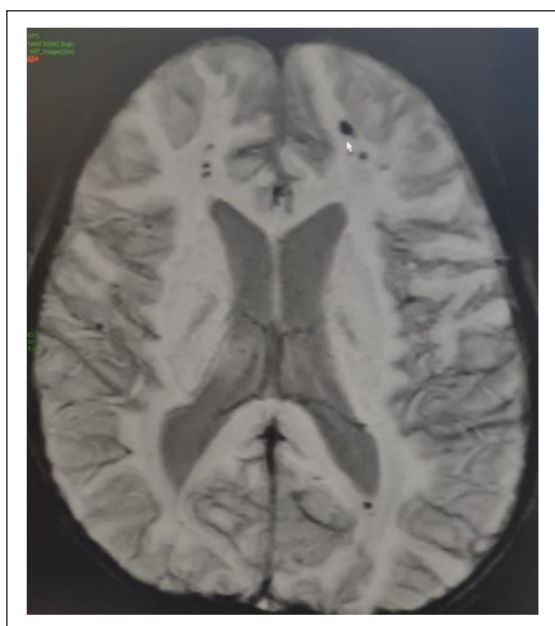


Figure 5. MRI of the brain: multiple microhemorrhages, white arrow pointing to largest one. MRI: magnetic resonance imaging.

Respiratory viruses were not detected on viral multiplex Polymerase Chain Reaction (PCR). Bacterial, fungal and tuberculous infections were ruled out in blood, respiratory secretions and BM. *Pneumocystis jirovecii* and Human Immunodeficiency Virus were negative by *Pneumocystis carinii* pneumonia stain and serological test, respectively. Parasites were excluded by serology and stool analysis. *Aspergillus* titre was elevated (1:320).

Autoimmune diseases were ruled out by the absence of antimitochondrial, anti-LKM (anti- liver, kidney microsomal antibody), anticardiolipin and antiglycoprotein antibodies; lupus anticoagulant; and normal levels of C3 and C4. The suspicion of vasculitis was unsupported as c-ANCA (antineutrophil cytoplasmic antibodies, cytoplasmic) and

p-ANCA (perinuclear antineutrophil cytoplasmic antibodies) were absent, although myeloperoxidase antibodies were reported as being equivocal. Fibrinogen (2.9 g/L) and D dimer (0.10 mg/L) levels were elevated during the acute phase, as well as total IgE (839 kU/L).

The multisystem involvement and possible vasculitic central nervous system (CNS) changes were suggestive of eosinophilic granulomatosis with polyangiitis (EGPA), although no skin manifestations were observed, and there was no prior history of asthma. Lung biopsy revealed fresh and old intra-alveolar haemorrhage with hemosiderin-laden macrophages with no evidence of granulomas or necrosis.

Treatment

The patient required intensive care including mechanical ventilation, blood product transfusion and hemodynamic support. He underwent three sessions of leucopheresis. Methylprednisolone pulse therapy was commenced at 30 mg/kg/dose for 3 days, followed by maintenance steroids.

Outcome and follow-up

The child responded well to the management. Following the sessions of leucopheresis, the WBC count gradually improved to 11,000 cells/mm³ with 25% EOs. But despite daily prednisolone therapy, WBCs as well as the percentage of EOs continued to increase (reaching a maximum of 60%) until administration of high-dose methylprednisolone, following which the EOs rapidly decreased to 1.7%. The patient was discharged on oral prednisolone. Neurological function improved gradually over the following 2 weeks to reach normal baseline status.

Upon follow-up after discharge, the patient was found to have improved dramatically with total recovery of neurological and respiratory function.

Discussion

HES is a rare entity in children.⁴ In 2011, the International Working Group on Eosinophilic Disorders (ICOG-EO) proposed a consensus on terminology and diagnostic criteria of various types of HES disorders.⁵

Mild blood eosinophilia is observed relatively frequently within the paediatric population, but persistent HE is uncommon and should prompt additional clinical evaluation,¹ which is a complex process requiring extensive investigations as HE could be secondary to a number of factors as discussed earlier. Less commonly, it may be primary, implying neoplastic or clonal disorder.⁶

Although lung involvement is relatively common, occurring in approximately 40% of IHES patients,⁷ associated ARDS is rare, with only a few cases described in the literature to date. Since HES is a reversible etiology of ARDS, the presence of eosinophilia in ARDS should never be ignored.⁸

Table 1. Learning points.

Learning points

- ▶ IHES, although rare, can lead to ARDS as well as multiorgan failure and requires vigilant management.
- ▶ Meticulous supportive treatment needs to be initiated early in the course of the disease to improve the outcome.
- ▶ High-dose corticosteroids dramatically influence the clinical course, although proper regimen and duration of treatment are not standardised.

IHES: Idiopathic Hypereosinophilic Syndrome; ARDS: Acute Respiratory Distress Syndrome.

The associated hyperleucocytosis may make the patient vulnerable to complications such as leucostasis and tumour lysis syndrome. The mode of treatment of HES often varies depending on etiology.

Paediatric data are derived mostly from adult case reports. The initial concept of HES was introduced by Hardy and Anderson⁹ in 1968, and the first diagnostic criteria of primary or idiopathic HES was suggested by Chusid et al.¹⁰ in 1975.

Striking leucocytosis with extreme eosinophilia invariably raises concern for the possibility of eosinophilic leukaemia. In 1941, Bass reported two paediatric cases where leucocytosis up to 51,000 cells/mm³ and eosinophilic percentage of 84% were encountered (malignancy was excluded in both cases).¹¹ In 1971, Rickles et al.¹² reviewed 16 cases of proposed eosinophilic leukaemia in children reported in the literature and raised serious concerns on the existing diagnostic criteria for eosinophilic leukaemia. Possibility of leukaemia was kept high for our patient too, but was ruled out by BM biopsy.

Among other possibilities, Churg-Strauss syndrome was also considered among the differentials, as supported by Mutsaers et al.,¹³ whereby a 13-year-old girl with pseudoleukemic differentiation was ultimately found to have a rare presentation of the same. But in our case, workup for underlying vasculitic etiology was negative.

Wang et al.¹⁴ have reported a similar case where a 4-year-old girl presented with hyperleucocytosis and HE (WBC count 225 k/ μ L with 96% EOs). The patient manifested only mild respiratory and cardiac dysfunction although plasmapheresis was done for persistent high leucocyte counts, and she was later diagnosed with IHES and represents the maximum reported leucocytosis pertaining to paediatric IHES. Although our patient presented with features of severe ARDS and also had neurological complications, he was considered to have IHES as all other investigations were inconclusive.

Khémiri et al.¹⁵ have described a 12-year-old boy with HE and acute eosinophilic lung disease with ARDS, associated with hyperleucocytosis of 45,380 cells/mm³ with 75% EOs (alveolar epithelial cells (AEC), 33,800 cells/ μ L), thus indicating that the magnitude of leucocytosis is not a predicting factor for development of ARDS.

The major drawback of this case report is that the possibility of EGPA could not be ruled out definitively as it shares many features with HES.¹⁶ The overlap eosinophilic

disorders include an association between HES and EGPA. Histopathologically confirmed CNS vasculitis in an adult with IHES was reported by Rice et al.,¹⁷ suggesting it as a new cause for CNS vasculitis, making the differentiation between these two entities more difficult.

Validity of the lung biopsy was questionable in our case as it was performed nearly a month after pulse steroid therapy, possibly influencing the histopathological features. Moreover, biopsy does not always reveal the characteristic pathological features. Alveolar haemorrhage with hemosiderin-laden macrophages is also described in ANCA-associated vasculitis; hence, we were not able to establish the diagnosis conclusively.

In our case, an excellent outcome was achieved in a child presenting with HE and severe ARDS due to early and aggressive management with leucopheresis and high-dose corticosteroid therapy. Being rare, HE in itself may not be recognised as an important trigger for ARDS and excluding underlying malignant etiology needs to be prioritised.

Conclusion

We report a rare case of HES in which the child presented with respiratory symptoms and unexplained hyperleucocytosis, soon going into ARDS requiring mechanical ventilatory support, several sessions of leucopheresis and also pulse steroid therapy, following which he had a dramatic recovery. Hence, although unusual, a finding of severe hypereosinophilia/hyperleucocytosis warrants extensive workup, bearing in mind the underlying possibilities including IHES.

Table 1 summarises the knowledge pearls gained from the case.

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Ethics approval

Ethical approval to report this case was obtained from King Saud Medical City's Institutional Review Board, reference number: HIRI-29-Oct20-01.

Informed consent

Written informed consent was obtained from a legally authorised representative (patient's father) for anonymized patient information to be published in this article.

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