Case report

Bilateral pulmonary nodules and intravascular pulmonary histiocytosis: A rare presentation of hemophagocytic lymphohistiocytosis secondary to Epstein-Barr Virus infection

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ABSTRACT

A 61-year-old male presented with worsening dyspnoea and constitutional symptoms for few weeks followed by bloody diarrhoea and loss and fever. Physical exam revealed tachycardia, respiratory distress, and splenomegaly without lymphadenopathy. Work up showed pancytopenia, hypoﬁbrinogenemia, acute kidney injury requiring haemodialysis, high ferritin level, positive IgG and IgM for EBV and positive soluble CD25. Chest CT scan showed bilateral pulmonary nodules. Lung biopsy showed intravascular pulmonary histiocytosis while bone marrow biopsy was negative for hemophagocytes. A diagnosis of hemophagocytic lymphohistiocytosis (HLH) was made based on fulﬁlling the diagnostic criteria and systemic steroids were initiated, which improved the patient’s condition gradually with resolution of dyspnoea, AKI and pancytopenia. Repeat chest CT scan showed resolution of bilateral pulmonary nodules. The patient was transferred to a tertiary centre to receive HLH-speciﬁc therapy. We present a rare presentation of HLH with steroid-responsive bilateral pulmonary nodules and a rare histopathologic ﬁnding of pulmonary intravascular histiocytosis, which has never been described in HLH or the lung tree.

1. Background

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease of overactive histiocytes and lymphocytes that can be inherited or acquired secondary to immunodeﬁciency, malignancy and infections. It can affect multiple organs, including the liver, spleen, lung and hematological system [1]. HLH is diagnosed based on HLH 2004 criteria issued by the Histiocyte Society, with ﬁve out of eight criteria needed to make the diagnosis (fever, splenomegaly, pancytopenia, hypertriglyceridemia and/or hypoﬁbrinogenemia, hemophagocytes in organ biopsy (bone marrow, spleen, lymph node, or liver), low or absent natural cell activity, high ferritin and high CD25) [2]. It may develop secondary to infection, with Epstein-Barr virus (EBV) being among the common reported culprits. Other associations include immunodeﬁciency and malignancies which were excluded in our case. Early diagnosis and management is important to reverse T cell overstimulation [1,2].

We present a rare respiratory presentation of HLH.

2. Case presentation

This is the case of 61-year-old male who had a past medical history of hypertension and right-sided hemicolectomy 6 months ago secondary to uncontrolled GI bleeding due to diverticulosis. He presented complaining of general weakness, fatigue, decreased appetite and dyspnoea of 2 weeks duration. His symptoms were associated with abdominal pain, bloody diarrhoea and low-grade fever. The patient had had a 20 lb weight loss in the last month. His physical examination was significant for tachycardia, moderate respiratory distress with tachypnoea requiring oxygen supply, bilateral diffuse crepitations on lung auscultation and splenomegaly without lymphadenopathy. Purpuric skin lesions were noticed in the lower abdomen and bilateral lower limbs.

Laboratory investigations showed pancytopenia, hypoﬁbrinogenemia, prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), mildly elevated liver enzymes, impaired kidney function with hyperkalaemia and metabolic acidosis, high ferritin and low C3. A chest CT scan showed bilateral pulmonary nodules (Fig. 1). There was evidence of splenomegaly on abdominal CT scan but no hepatomegaly. Immunological workup; auto-antibodies including antinuclear antibody (ANA), Anti-Neutrophil Cytoplasmic Antibodies (ANCA), anti-glomerular basement membranes, cryoglobulin and quantitative immunoglobulin, infectious workup (Histoplasma and Blastomyces antigens, hepatitis B and C and HIV) and cancer screening (tumour markers, CT scan of the chest, abdomen and pelvis and protein electrophoresis) were all normal. IgG and IgM antibodies to Epstein-Barr Virus (EBV) were positive with elevated CD25. Lung biopsy showed intravascular histiocytic cells (Figs. 2–3). Histiocytic cells are...
positive for CD-168 on immunohistochemical staining (Fig. 4). Special stains for pathogenic organisms for granulomatous inflammation are negative, as well, there was no evidence of necrotizing vasculitis or malignant cells. Renal biopsy showed features of acute tubular necrosis. There was no evidence of hemophagocytes or malignancy on bone marrow biopsy.

The patient was admitted to the hospital and he was started on broad-spectrum intravenous antibiotics with supportive treatment for his respiratory insufficiency, acute kidney injury, disseminated intravascular coagulopathy (DIC) and gastrointestinal (GI) bleed. The patient's condition worsened as he continued to have GI bleeding requiring blood products transfusion, haemodialysis was started, and he required non-invasive ventilation for worsening respiratory failure. The patient was started on high-dose methylprednisolone after discontinuation of antibiotics given the negative cultures and no identified source of infection.

A diagnosis of HLH with pulmonary intravascular histiocytosis (IVH) secondary to EBV infection was made. The patient was started on systemic steroids with high-dose intravenous methylprednisolone, after which his condition improved gradually with resolution of his dyspnoea, GI bleeding, DIC, pancytopenia and kidney injury with haemodialysis no longer required. Repeat chest imaging 10 days later showed significant improvement of his lung nodules (Fig. 5). The patient was transferred to a tertiary facility to receive HLH-specific therapy where our diagnosis was supported, and he was started on etoposide in addition to steroids.

The patient was followed up and his condition had been stable after initiation of proper treatment until 2 months later, when he experienced a relapse of his disease. The patient declined any further treatment, he preferred hospice care and unfortunately died few months later.
3. Discussion

Our case report illustrates a rare pulmonary presentation of HLH with newly described histopathological findings in patients with HLH. Our patients fulfilled the criteria for the diagnosis of HLH as he had fever, splenomegaly, hypofibrinogenemia, pancytopenia, high ferritin level and elevated CD 25. Our diagnosis was supported by a tertiary facility with HLH specific centre. The diagnosis of malignancy like lymphoma which may mimic this presentation was ruled out to a reasonable degree as there were no evidence of lymphadenopathy or solid organ malignancy on computed tomography, as well, bone marrow biopsy didn’t reveal any evidence for haematological malignancies and tumour screening markers were negative.

Our patient presented with dyspnoea and a chest CT scan showed diffuse bilateral pulmonary nodules involving the whole lung field bilaterally, which has never been described in patients with HLH syndrome with lung disease. Pulmonary involvement was noticed in 54% of patients with HLH admitted to hospitals in France over 14 years [3]. In the same retrospective analysis, alveolar interstitial infiltrates without distinct patterns were often seen during radiographic examinations. Additionally, about 50% of the patients had pleural effusions and mediastinal lymphadenopathies [3]. Another review involving more than ten case series and 775 patients reported 42% of patients with HLH had pulmonary involvement [4]. Pulmonary involvement in patients with HLH carried a poor prognosis; in comparison to those with no lung involvement, patients with pulmonary involvement had a higher hospital mortality (52.5% vs 20%) [3].

Another rare finding in our patient is the intravascular histiocytosis (IVH) which was evident in the lung biopsy. Hemophagocytes can be found in the lungs, like in other organs, but it is not part of the diagnostic criteria. In Seguin et al.’s case series, detailed analysis of 44 HLH patients’ bronchoalveolar lavage fluid did not find any eosinophil infiltration or alveolar haemorrhage but did reveal malignant lymphoma infiltration in one case. Additionally, five patients underwent lung biopsy and were found to have tuberculosis, T cell lymphoma and Kaposi sarcoma, but not hemophagocytes or histiocytes [3]. In our patient, bronchoalveolar lavage fluid was negative, but lung biopsy showed pulmonary IVH, a rare finding which has never been reported in patients with pulmonary HLH or in the lung tree before. Intravascular histiocytosis was reported under different names, like intralymphocytic histiocytosis, nodular mesothelial/histiocytic hyperplasia and others, in Michal et al.’s review of 50 cases with this rare histopathological finding. None of these findings were reported in the lung parenchymal tissues, while common places were the peritoneum and skin lesions [5]. Similarly, a case series of 16 patients with intravascular histiocytosis reported all 16 cases were associated with cutaneous lesions and rheumatoid arthritis had been diagnosed earlier in 5 of them [6].

The significance of this association between HLH and IVH is yet to be determined since literature is lacking.

Learning points

- HLH is a multisystem disease which could be fatal.
- We described a rare respiratory presentation of HLH with bilateral pulmonary nodules which were responsive to steroids.
- Interestingly, our histopathologic finding of intravascular histiocytosis has never been described in the lung tree, which was identified in our patient.
- The significance of this association between HLH and IVH is yet to be determined since literature is lacking.

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2018.10.029.

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