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HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS TRIGGERED BY CYTOMEGALOVIRUS REACTIVATION IN AN IMMUNOSUPPRESSED PATIENT WITH PAUCI-IMMUNE GLOMERULONEPHRITIS

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ABSTRACT

We report on a 67-year-old male patient admitted to the Internal Medicine department for fever, joint pain and exertional dyspnoea. Two months before his admission, the patient had been diagnosed with pauci-immune necrotising glomerulonephritis, for which he had been treated with rituximab and corticosteroids.

Upon admission the patient was stable, but within a few hours he became unstable as liver failure and acute cytopaenia occurred. Blood investigations revealed cytopaenia, altered coagulation tests, high ferritin, triglycerides, lactate dehydrogenase and C-reactive protein levels, and severe cytocholestasis. A liver echography was normal. The patient had been transferred to the intensive care unit to receive supportive support when the cytomegalovirus polymerase chain reaction (CMV-PCR) test came back positive. The diagnosis of haemophagocytic lymphohistiocytosis associated with a CMV infection and/or reactivation in an immunosuppressed patient was made. Specific treatment was administrated, along with symptomatic treatment. The patient clinically improved during hospitalisation with complete resolution of symptoms.

KEYWORDS

Haemophagocytic lymphohistiocytosis, cytomegalovirus, immunosuppression

LEARNING POINTS

- Haemophagocytic lymphohistiocytosis (HLH) is a rare disease yet important to diagnose, as it is quickly life-threatening.
- The diverse symptoms of HLH can make diagnosis tricky, with many potential causes. As clinical presentation is not very specific, it is often mistaken for infection with severe sepsis and its diagnosis is often delayed.
- Limited understanding of this condition could lead to worse outcomes for patients. Recognising it early is crucial for starting the right treatment and enhancing both the well-being and survival chances of those affected by this complex disorder.
- In practice, HLH must be suspected when bi/pancytopaenia occurs in a patient presenting a high fever of unknown cause, especially when they have a history of immunosuppression. Managing it often requires a range of approaches, such as intensive care, immune system suppression, specialised medications or even stem cell transplants.

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INTRODUCTION

Haemophagocytic syndrome or haemophagocytic lymphohistiocytosis (HLH) arises from an overactive yet uncontrolled immune response, leading to intense inflammation. Key indicators include fever, enlarged liver and spleen, low blood cell counts and widespread infiltration of histiocytes in tissues. Many patients have low blood pressure, which does not respond to fluid therapy. The liver and spleen are the organs most frequently involved in HLH with high levels of aspartate aminotransferase, alanine aminotransferase and/or bilirubin, leading to fulminant hepatitis or liver failure. This syndrome manifests in two primary forms: a hereditary form (HLH disease) emerging in early childhood, and a reactive form occurring at any age, often associated with infections, cancers or autoimmune disorders, particularly in individuals with weakened immune systems (HLH mimics). In adults, HLH mimics are more prevalent than HLH disease. Reactive haemophagocytic syndrome poses a serious threat to life, with mortality rates ranging from 20 to 60% in adults. Early diagnosis is critical, as prompt initiation of appropriate treatments can enhance survival rates. Nevertheless, diagnosing HLH proves challenging due to the absence of distinct clinical, biological or pathological characteristics.

CASE DESCRIPTION

A 67-year-old man was admitted to this hospital because of fever, joint pain and exertional dyspnoea. Two months previously, the patient had been referred to the nephrology consultation for a rapid deterioration of renal function and following an extensive diagnostic workup, including a renal biopsy, he was diagnosed with anti-myeloperoxidase positive, rapidly progressive pauci-immune necrotising glomerulonephritis. The patient was treated with rituximab and corticosteroids. One month after his second rituximab injection, the patient began to feel unwell. For two weeks he was feeling asthenic, presented fever and chills, and was short of breath. Examination revealed a temperature of 38.6°C, blood pressure of 96/61 mm Hg, heart rate of 92 beats per minute and oxygen saturation of 98% on ambient air. Auscultation revealed slight hypoventilation and fine crackles in the right lung base. Red cell and platelet counts were low with a haemoglobin of 11.5 g/dl, and 92,000 platelets per microlitre. The white cell count was normal. A slight hepatic cytolysis appeared, with a stable renal function; C-reactive protein was high (98 mg/l). Urine tests, chest radiography and a computed-tomography scan of the abdomen showed no sign of infection. The patient received empiric antibiotics and was admitted into the Internal Medicine department, where diagnostic tests were performed.

In 48 hours, the patient became unstable with haemoglobin counts dropping to 8.2 without any clinical signs of haemorrhage. Coagulation tests became altered, with a partial thromboplastin time dropping off to 57% and an activated partial thromboplastin time going up to 44.5 s. Ferritin levels and cytocholestasis increased tenfold, high hypertriglyceridaemia was measured and C-reactive protein doubled. As hepatic dysfunction had occurred, an echography was performed but showed no abnormalities. Blood pressures were labile while remaining low. Oxygen saturation dropped off, and the patient needed 2 litres/min of oxygen to stay eupnoeic. The spectrum of antibiotics was broadened, and the patient was admitted to the intensive care unit (ICU) to receive vasopressive support. Blood cultures came back negative, serologies were negative for hepatitis B, hepatitis C virus, brucellosis and leptospirosis, but indicated past infections for Epstein-Barr virus, cytomegalovirus (CMV), toxoplasmosis, hepatitis A and herpes simplex virus. The patient stayed in the ICU for about two weeks, where he first received supportive care (antipyretics, fluids, noradrenaline, transfusions). As soon as the PCR test came back positive for CMV, valganciclovir was administrated alongside symptomatic treatment, and the patient showed a rapid clinical improvement.

DISCUSSION

A real-time PCR test confirmed a CMV infection, with >13 000 copies; this is compatible with either a reactivation of his past CMV infection or a primo-infection of another type of CMV. The HScore was calculated at 204 points in this patient, with a high probability of haemophagocytic syndrome (88–93%). The diagnosis of HLH associated with a CMV infection and/or reactivation in an immunosuppressed patient was made.

HLH is a broad syndrome which can occur at any age, and typically develops in the setting of infectious, malignant or rheumatological diseases. It is rarely a manifestation of underlying genetic inborn errors of immunity that predispose to immune dysregulation. Diagnostic criteria lack both sensitivity and specificity; recognising the presenting features and making a diagnosis are often challenging. This syndrome includes two different entities important to distinguish as they require entirely different treatments. Conditions that would benefit from HLH-directed immunosuppressive therapies are termed HLH disease, and those conditions that would not benefit from such therapy are termed HLH disease mimics[1]. When HLH is suspected, mimickers of HLH disease (HLH triggered by infections or other immune activating events) should be ruled out as direct treatment of the infection (if present) is preferable to HLH-directed immune suppression, which can potentially worsen the underlying infection[2].

CMV colonisation – which can trigger massive T-cell activations causing a cytokine storm and macrophage activation – can induce HLH, leading to haemophagocytosis and inflammatory tissue damage. Immunosuppression is a common denominator for patients at risk for CMV-induced HLH[3].

HLH must be suspected when bi/pancytopaenia occurs in a patient presenting with a high fever of unknown cause, especially if they have a history of immunosuppression.

Criteria associate fever, splenomegaly, cytopaenia, increased triglycerides/decreased fibrinogen, neurologic involvement, stigmata of liver dysfunction and haemophagocytosis[1-4]. Other non-specific clinical manifestations such as oedema, rashes and gastrointestinal symptoms, for example diarrhoea, nausea, vomiting and abdominal pain, may also be seen[3]. Complications are severe (sepsis, bleeding, multi-organ failure). T-cell activation is central to HLH pathogenesis, leading to elevated sCD25 observed in untreated HLH. In the same way, HLH appears to be largely driven by interferon gamma (IFN-γ), and elevations of CXCL9 should be seen in untreated cases[5-7]. Elevated expression of granzyme B in natural killer cells has been shown to be similarly ubiquitous in HLH[2].

Numerous proinflammatory cytokines are seen in HLH that include IFN-γ, TNF-α, IL-1 β, IL-2, IL-6, IL-12, IL-16 and IL-18[5-7]. Overactive immune cells invade organs and hypersecretion of cytokines result in organ failure[2]. Gene mutations can be found in individuals of any age and with any family history[1]. Haemophagocytosis can be confirmed in a bone marrow examination or in a biopsy of the involved organ. Pathologic evaluation and recognition of haemophagocytic histiocytes is a key component of the diagnosis; however, published literature suggests that marrow evaluation for haemophagocytic histiocytes has a poor correlation with disease probability overall[1].

In this case, the patient experienced clinical improvement in supportive and antiviral treatment, which confirm the diagnosis of HLH disease mimics (induced by CMV activation). Currently, the standard of care for HLH should be considered to be treatment with etoposide and dexamethasone[1]. In general, immediate treatment of HLH is warranted once a diagnosis is made, while it is important to rule out HLH disease mimics or malignancies before starting therapy (if possible). An important risk of prolonged immunomodulating treatment is possible reactivation of the triggering infection. The therapeutic challenge of suppressing hyperinflammation while maintaining control of the underlying infection must be considered when treating HLH patients[3]. Regular monitoring of immune activation, via measurement of sCD25, is essential to gauge the success of therapy and need for treatment reintensification or alternative salvage approaches. Patients with HLH frequently reactivate as steroids are weakened, so close clinical and regular laboratory monitoring should continue as long as patients are receiving treatment. Emapalumab, an IFN-γ blocking monoclonal antibody, was recently approved for refractory or recurrent HLH[1]. Allogeneic haematopoietic transplantation is performed to prevent potentially fatal HLH disease recurrence in patients with clear family histories and/or genetic aetiologies for HLH[2].

CONCLUSION

Haemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal disease process that is caused by a constellation of genetic predispositions, changes in immune status and triggers, all of which result in sustained CD8+ T-cell activation. Due to the rarity, diversity and complexity of HLH syndrome, diagnosis is difficult and often delayed. Recognition decreases the risk of misdiagnosis and inappropriate treatment. The distinction of HLH disease and HLH disease mimics within the broader syndrome of HLH will aid physicians in considering all relevant diagnostic considerations and following the cases, to avoid unnecessary or harmful immune suppression.

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