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Case Report

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Nonresolving Pneumonia with Impaired Liver Function and Hyperferritinaemia

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ABSTRACT

Haemophagocytic syndrome is a differential diagnostis of sepsis that requieres rapid diagnosis to initiate treatment as the patient can suffer a rapid deterioration. We present a case with inicial diagnosis of multilobar pneumonia with excellent overall condition but jaundiced and with platelopenia, anaemia, hyperferritinemia who rapidly evolves to death with its autopsy compatible with T Lymphoma, Epstein-Barr positive with cytotoxic phenotype.

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Introduction

Haemophagocytic syndrome (HPS) or Haemophagocytic Lymphohistiocytosis (HLH) is a severe and rare state of immune activation, classified as primary and secondary to triggers such as autoimmune diseases, infections or neoplasms. Both primary and secondary HPS can be rapidly fatal and require early diagnosis and specific immunosuppressive treatment. Patients show rapid clinical deterioration, fever, hepatosplenomegaly, coagulopathy, hepatic failure, cytopenia, hyperferritinaemia and decreased/absent NK cell cytolytic activity [1].

Clinical Case

A 72-year-old male with no relevant personal history, no toxic habits, of Italian nationality, living 6 months of the year in Gran Canaria and the rest in Vicenza (Italy) for years. He worked as a representative and is currently retired. He came to emergency department for intermittent fever of three weeks' duration, associated with dry cough and no other symptoms, relating the fever to previous ingestion of seafood. He had previously been treated with Amoxicillin-Clavulanic acid and Azithromycin. He arrived at the emergency department in good general condition, feverish, haemodynamically stable, with cutaneous and mucosal jaundice and hepatomegaly. The X-ray showed faint alveolar infiltrates and the blood tests showed cholestasis with ALT 164 U/L, AST 302 U/L, GGT 200 U/L, with elevated bilirubin of 3.79 mg/dL, predominantly direct, LDH 749 U/L, C reactive protein 2.53 mg/dL, procalcitonine 2.13 ng/mL, normal renal function and ions, platelets 61000/µL, haemoglobin 12 g/dL without leukocytosis. Broad-spectrum antibiotics (Meropenem and Linezolid) and corticosteroids at intermediate doses were administered, cultures for pneumonia were requested and the patient was admitted to pneumology ward with a diagnosis of multilobar pneumonia. Laboratory tests were expanded to include autoimmunity, hepatitis serology and fever of unknown origin. Initial evolution was favourable, with remission of fever and good general condition, but the persistent worsening of liver function was noteworthy, in addition to persistent plateletopenia of around 70000/uL and mild progressive anaemia of up to 9 g/dL with normal MCV and MCH, with no signs of bleeding, associated with very high ferritin of 19488.ng/mL. The digestive department requested extended analysis and considered toxic hepatitis due to Amoxiclinic-Clavulanic acid and infectious hepatitis as the most likely diagnostic options. A chest-abdomen CT scan was performed with findings of alveolar infiltrates suggestive of bilateral multilobar pneumonia with moderate amounts of bilateral pleural effusion, slight amounts of ascitic fluid and hepatosplenomegaly with splenic infarcts. A bronchoscopy was performed, observing icteric bronchial mucosa and no other endoluminal alterations, and bronchoalveolar lavage was performed in the middle lobe, with negative cultures and cytology. Ten days after admission, he presented a new fever peak, and antibiotics were reintroduced, requesting assessment by the infectious diseases unit, which recommended treatment with Meropenem and Doxycycline, again requesting extensive laboratory tests, serology and blood cultures, assessing three most likely diagnostic options: zoonosis, HPS and nosocomial pneumonia. The only positive serology results were IgG against CMV, EBV, HVH type 1 and 2, VZV, measles and Toxoplasma. Since the febrile upturn, the patient had tended to hypotension with sinus tachycardia between 100 and 110 bpm, with preserved diuresis but worsening renal function, frank worsening of liver function, with bilirubin values reaching 20. 41 mg/dL, always at the expense of direct bilirubin, transaminases 327 mg/dL (ALT) and 642 mg/dL (AST), GGT 575 mg/dL, which had remained stable until then, reactive C protein 4.76 mg/dL and procalcitonine 14.52 ng/mL, and it was decided to prescribe serum therapy and corticoid boluses. In the following days, he again presented several febrile peaks with persistent analytical alterations, assessing a non-infectious aetiology as the patient suffered from asthenia with no other symptoms realated to any organs. A cranial CT scan was completed in view of the presence of

motor and speech slowness, without observing acute brain lesions or bleeding. A liver biopsy was performed and the patient was evaluated by the haematology department, with a high suspicion of HPS (he met 5 out of 8 of the clinical diagnostic criteria for haemophagocytic syndrome (Protocol HLH-2004, table 1) and a bone marrow biopsy was requested.

Table 1: Haemophagocytic Syndrome Criteria [4]

HLH-2004 diagnostic criteria of which at least five must be fulfilled.

- Ferritin ≥500 µg/L.
- Fever (≥38.2°C).
- Splenomegaly.
- Cytopaenias in ≥2 lines (haemoglobin <90 g/L, platelets <100×10^9/L, neutrophils <1.0×10^9/L).
- Hypertriglyceridaemia and/or hypofibrinogenaemia (fasting triglycerides ≥2.65 g/L, fibrinogen <1.5 g/L).
- Haemophagocytosis in bone marrow or spleen or lymph nodes.
- Low or absent natural killer cell activity.
- Soluble CD25 (soluble interleukin-2 receptor) ≥2400 U/mL.

HLH, haemophagocytic lymphohistiocytosis.

He had rapid clinical deterioration with marked tachypnoea secondary to severe metabolic acidosis, renal failure, coagulopathy, liver failure. Perfusion of bicarbonate, amphotericin B, dexamethasone and Levofloxacin were initiated, and he was transferred to the intensive care unit, where he died a few hours later. Given the fulminant fatal link without a diagnosis, an autopsy was requested, and the histological analysis was compatible with T Lymphoma, Epstein-Barr positive with cytotoxic phenotype with involvement of: liver, spleen, myocardium, lungs, thyroid, kidneys, adrenal, small intestine, bladder, prostate and brain; in addition to presenting diffuse alveolar damage, focal glomerulosclerosis, severe aortic atherosclerosis and common left trunk, splenic infarcts.

Discussion

The differential diagnosis between HPS and sepsis is crucial. Once the diagnosis has been established, all therapeutic decisions must be made because on the one hand, an early aggressive immunosuppressive treatment such as Dexamethasone, Etoposide and Cyclosporin A, or even haematopoietic stem cell transplantation in SHF, while sepsis is treated with antibiotic therapy [2].

The hyperinflammation that is present in both situations leads to overlapping clinical scenarios including fever and deterioration of general condition. To complicate the situation, HPS can also be complicated by sepsis [2]. As there is no typical marker for HPS, the 8 criteria for HLH must be considered, the most important being hyperferritinaemia especially when it is very high over 2000 ng/mL [2]. Marrow biopsy to check for haemophagocytosis should be performed when 4 of the 8 criteria are met, and is theoretically not essential when 5 of 8 are met, but the initiation of immunosuppressive treatment, even corticosteroids alone, may make subsequent diagnosis of malignancy difficult or impossible. There is discord in the literature; according to some studies biopsy is strongly recommended in all situations, in others having 4 criteria, one of these being ferritin, it is not necessary given the demonstrated association with ferritin levels and haemophagocytosis in critically ill patients [2-5]. In most cases of sepsis only 1 or 2 criteria are met, whereas HPS requires a minimum of 5 out of 8 [2]. The HLH-2004 criteria were developed in children, but have proven to be useful in the diagnosis of critically ill adults as well [3,4]. In the literature we have not found cases like our patient with T-cell lymphoma debuting with symptoms suggestive of pneumonia and progressing to HPS, and of course this is an exceptional case in a pulmonology ward, which is why we consider it to be of interest [6].

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