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HIV Infection Presenting as Haemophagocytic Syndrome

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Abstract:

The authors describe a case of a 48-year-old man who presented with four weeks of fever, generalized malaise, weight loss, right upper quadrant abdominal pain and hepatosplenomegaly. He evolved with pancytopenia, bone marrow haemophagocytosis and hyperferritinaemia. Recent diagnosis of HIV infection, with the exclusion of other plausible causes, prompted the diagnosis of haemophagocytic syndrome (HPS) secondary to HIV. Despite intensive care support and initiation of antiretroviral therapy, the patient died. HPS diagnosis secondary to HIV alone demands the exclusion of all the other secondary causes. The best approach includes early diagnosis and specific treatment of the associated cause, whenever possible.

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Introduction

Haemophagocytic syndrome (HPS) is a rare and potentially fatal disorder [1]. Its primary form is associated with underlying genetic abnormalities, usually presenting in childhood. Secondary HPS appears most frequently in the setting of infection, malignancy or autoimmune disease [2, 3]. This type usually presents in adults and has a better prognosis.

Probably underestimated, secondary forms are still being identified. In this setting, HIV has been associated with HPS with a wide range of disorders, namely viral, bacterial, mycobacterial, fungal and protozoal infections, malignancy, autoimmune diseases, related therapy and even HIV itself [1]. The diagnostic guidelines proposed by the Histiocyte Society have contributed to clarification of the diagnosis [4]. Naturally, the diagnosis of HPS secondary to HIV infection is only possible in the absence of other plausible causes. The authors report a HPS secondary to HIV and discuss some particular aspects.

Case report

A 48-year-old heterosexual man was admitted to the hospital after four weeks of fever, generalized malaise, weight loss and a right-upper quadrant abdominal pain. Besides smoking and a considerable alcohol intake (80–110 g/day), he had no significant travel, drug or medical history. On admission, the patient appeared acutely ill, with mild confusion, fever and hypotension, without other abnormal physical findings. Laboratory tests (*Table 1*) showed 87,000/mm^3 platelets (150,000–400,000/mm^3), normochromic and normocytic anaemia (Hb=7.4 g/dl), lymphopenia (860/µl) (1500–4000/mm^3), elevated C-reactive protein (157 mg/l) (<1.0 mg/l), low albumin (2.5 g/dl) (3.0–5.0 g/dl), international normalized ratio (INR) of 1.3 and elevated serum ferritin levels (7867 ng/ml) (12.8–454 ng/ml).

Variable	Reference range	Day 1	Day 9 (Day 1 HAART)	Day 19 (Day 10 HAART)
Haemoglobin (mg/dl)	13–17	7.4	6.8	4.2
Leucocytes (/mm^3)	4,000–11,000	2,900	2,620	2,520
Neutrophils (/mm^3)	2,000–7,500	2010	2120	1,590
Lymphocytes (/mm^3)	1,500–4,000	860	210	630
Platelets (/mm^3)	150,000–400,000	87,000	<10,000	<10,000
INR		1.3	1.4	1.6
Fibrinogen (mg/dl)	220–450	402	307	–
Ferritin (ng/dl)	12.8–454	7,867	3,049	2,109
Triglycerides (mg/dl)	40–160	151	52	–
Albumin (g/dl)	3–5	2.5	1.8	1.7
Total bilirubin (mg/dl)	0.2–1.00	0.3	9.9	4.1
Aspartate aminotransferase (U/l)	10–34	27	32	32
Alanine aminotransferase (U/l)	10–44	8	7	16
Alkaline phosphatase (U/l)	45–122	58	37	79
γ-Glutamyl transpeptidase (U/l)	10–66	17	12	51
Sodium (mmol/l)	135–145	144	153	167

Table 1: Laboratory data

Chest radiography showed small bilateral pleural effusions, confirmed by ultrasound, which also revealed homogeneous mild hepatosplenomegaly and moderate ascites. Thoracoabdominal CT also showed diffuse lympadenopathy (*Fig. 1*).

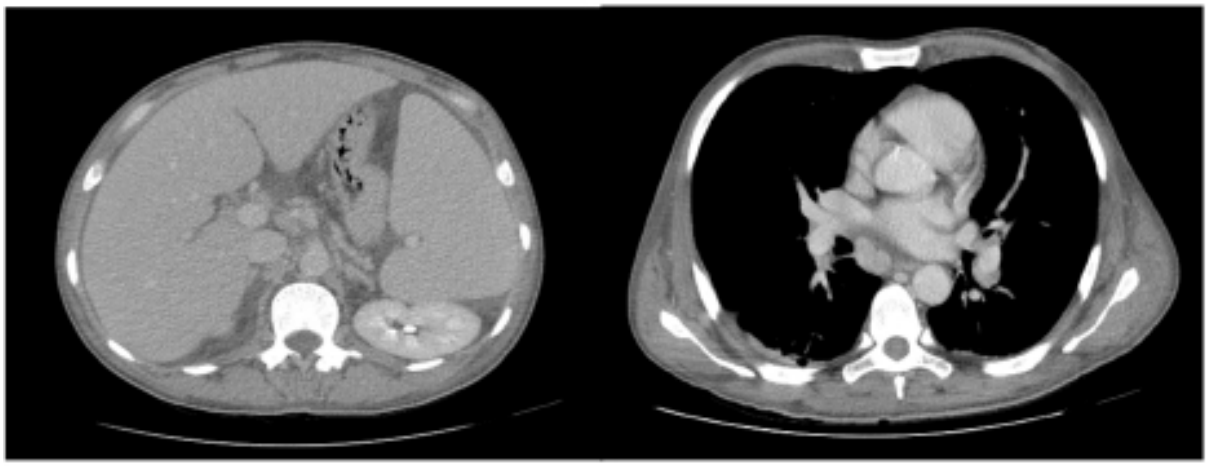

Figure 1: Thoracoabdominal CT with diffuse lympadenopathy (<2 cm) and homogeneous mild hepatosplenomegaly.

Peritoneal fluid was tested and showed an exudate with an elevated mononuclear count, low adenosine deaminase and negative PCR for *Mycobacterium tuberculosis*. HIV testing was positive with HIV RNA of 101,000 copies/ml, and a TCD4 cell count of 38/mm^3 (2.4%).

Serology for syphilis, *Brucella*, Epstein–Barr virus, cytomegalovirus, *Toxoplasma gondii* and hepatitis A, B and C was negative.

At this point, considering the recent HIV diagnosis, with severe immunosuppression and a presentation of a systemic illness (haematologic findings, pleural and peritoneal effusions and signs of activation of the reticuloendothelial system), haematological malignancy, tuberculosis and hepatic disease were hypothesized as the most probable differential diagnosis. Nevertheless, a sepsis also had to be considered and the patient was admitted to the intermediate care unit and started on broad-spectrum antibiotic therapy.

A bone marrow sample was obtained and showed features of hypocellularity and haemophagocytosis (*Fig. 2*) but no evidence of malignancy.

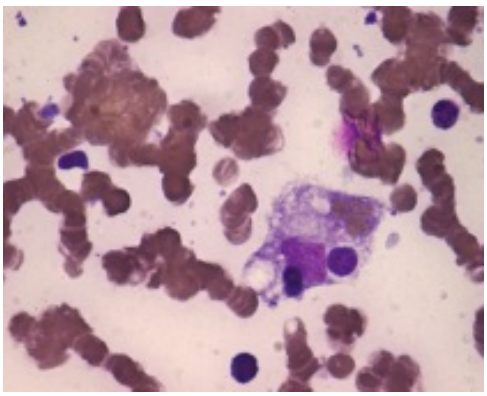

Figure 2: Bone marrow with macrophage phagocytosis of erythroblasts (×100 Giemsa stain)

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The analysis of blood, bone marrow and lymph node tissue showed no sign of lymphoproliferative disorder and was negative for bacteria, mycobacterium and fungi.

On the fourth day of inpatient care, despite broad-spectrum antibiotics, the clinical state of the patient deteriorated with multiple organ failure and he was admitted to the intensive care unit, requiring vasopressor support and invasive mechanical ventilation.

A diagnosis of haemophagocytic syndrome, most probably related to HIV infection, was assumed, since no evidence of other infection or haematologic disease was found. The patient was started on HAART (tenofovir, emtricitabin, lopinavir/ritonavir), prednisolone (1 mg/kg daily) and immunoglobulin (1 g/kg for two consecutive days).

Haematologic dysfunction evolved with deteriorating pancytopenia, liver dysfunction with progressive hypoalbuminaemia and hyperbilirubinaemia and prolongation of INR. He also developed a state of increased vascular permeability, unresponsive to albumin administration, and associated refractory shock.

Despite all the above treatments, the patient's clinical state continued to deteriorate and death occurred at day 10 of HAART.

Discussion

The pathophysiology of HPS is best understood for the primary form of HPS, in which genetic defects in proteins that play an important role in cytolytic secretory pathway [7] lead to excessive activation of T cells and subsequently to increased cytokine secretion and hyperactivation of macrophages [1]. The pathogenesis of secondary HPS is less clear and in the setting of HIV infection it is probably related to acquired defects in cellular cytotoxicity [1].

Clinical features of HPS are consistent with this state of immune hyperactivation, including fever, lymphadenopathy, hepatosplenomegaly and jaundice, as well as cytopenia and impaired liver function. These nonspecific features have a wide differential diagnosis in the context of HIV. Indeed HPS may be mistaken for many other disorders, most frequently lymphoproliferative diseases or infections. In this case the acute clinical presentation suggested a septic status although with an inconsistent evolution (no response to broad-spectrum antibiotic therapy, vasopressor support and albumin infusion). Efforts to exclude infections and lymphoproliferative disorders were made. The clinical findings of fever, hepatosplenomegaly, cytopenias, bone marrow haemophagocytosis and hyperferritinaemia, fulfilled five of the above-mentioned criteria, suggesting HPS as the most probable diagnosis. No trigger but HIV was found. The main aetiology for HPS in HIV patients is infection. In the largest study to date, only 5% of patients were found to have no underlying cause of HPS other than HIV itself [5].

The proposed management for the primary form of HPS, the HLH-94 protocol [4], has proven efficacy in Epstein–Barr virus-associated HPS but not in HIV infection. For HPS associated with HIV

infection, treatment should be individualized, with supportive care promptly initiated and treatment of potential triggers. The potential efficacy of HAART has been described [1], although the risk of immune reconstitution syndrome should be considered. Also, high-dose corticosteroids are commonly used as well as intravenous immunoglobulin (IVIg) [1]. In this case, supportive care, empiric broad-spectrum antibiotics, corticosteroid therapy, IVIg and HAART were instituted, none with any obvious beneficial effect.

The prognosis of HPS was significantly improved after HLH-94 introduction for primary forms [15]. A mortality rate of 31% at 3 months for HPS associated with HIV has been described [5]. Prognostic factors in the setting of HPS associated with HIV are still to be identified, although ICU admission, cytopenias and haemotological/malignancy-associated disorders are expected to be relevant. Specifically related to HIV, low CD4 cell count is expected to be a possible prognostic indicator.

Conclusion

HPS diagnosis is complex and in the context of HIV infection still constitutes a great challenge. The best approach seems to include adequate identification of prognostic factors, early diagnosis and specific treatment of the associated cause, whenever possible.

Learning Points

- HPS diagnosis is complex and in the context of HIV infection still constitutes a great challenge.
- Diagnosis of HPS secondary to HIV alone demands the exclusion of all the other known secondary causes of HPS.
- The best approach to treat HPS includes early diagnosis, adequate identification of prognostic factors, supportive care and specific treatment of the associated cause, whenever possible.
- Consider HIV as a possible cause of HPS where no other cause has been identified.

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