VIRAL ASSOCIATED HAEMOPHAGOCYTIC SYNDROME - A POST MORTEM DIAGNOSIS

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Introduction

The clinical and autopsy findings in a young serving soldier, who was hospitalised as a case of pyrexia of unknown origin with hepatosplenomegaly, are presented. Unfortunately, the final diagnosis of viral associated haemophagocytic syndrome (VAHS) could only be established after autopsy.

VAHS is a benign disorder characterized by systemic proliferation of haemophagocytic histiocyte and its precursors [1]. It is commonly associated with acute systemic viral infections like *Epstein-Barr*, *Cytomegalovirus*, *Herpes simplex*, *Varicella zoster*, *Adeno* and *HIV* viruses [2,3,4]. Initially, Risdall et al in 1979 [5], in their original report found the association of these cases with viral infections but in their later study of the cases, no such proven association could be established [3].

This case of VAHS is reported because of its rarity and difficulties in establishing the diagnosis by unwary clinicians. Secondly, in addition to wide spread proliferation of haemophagocytic histiocytes in various organs, the lymph nodes showed extensive necrosis with marked lymphoid depletion, which is an uncommon finding [4].

Case Report

A 18 year old serving soldier was admitted to a service hospital with complaints of high-grade fever of 10 days duration. Fever ranged from 101-104°F, it was associated with rigor and chills, headache and at times episodes of vomiting. There was no history suggestive of upper respiratory or urinary tract infection, bowel disturbances or deep-seated abscess. However, he had similar complaints six months back for which he was treated, but he did not know the details of the treatment. On clinical examination, besides fever, he had pallor and tachycardia. Chest radiograph was unremarkable. Liver was enlarged by 2 cm and spleen 16 cm. At admission the haemoglobin (Hb) was 7 gm/dl, total leukocyte count 4,200/cmm with 45% neutrophils and platelet count 1,20,000/cmm. Blood urea, serum creatinine and SGOT were

within normal limits. SGPT was raised to 80 IU/dl. Liver function tests, Widal test, VDRL, ANF and urine examination were within normal limits. Three sets of blood cultures were negative. Bone marrow aspiration was reported as normocellular with no mention of histiocytes.

He was treated with broad-spectrum antibiotics, antimalarial drugs, corticosteroids and blood replacement. During the period of his hospitalization, the general condition rapidly deteriorated. Within a week, the Hb level fell down to 6 gm/dl inspite of blood replacement, TLC progressively decreased to 2,000/cmm and platelet count to 80,000/cmm. He terminally experienced nausea and vomiting, passed dark coloured stool, had haematemesis and died within a fortnight.

Gross autopsy findings

The autopsy was conducted after 30 hours of death. Rigor mortis had passed off and pallor was evident. Pleural and abdominal cavities contained about 100 ml of blood-tinged fluid. Lungs were congested, edematous and bulky. Blood-tinged frothy fluid exuded on cut section. The mediastinal and hilar group of lymph nodes were enlarged. Stomach contained small quantity of black coloured fluid, however, the mucosa was intact. Liver was reddish brown in colour, large in size and weighed 2,500 g. There were multiple enlarged mesenteric lymph nodes, the largest measured 3x2.8 cm. On cut section, the lymph nodes showed wide spread areas of necrosis. Four inches segment of the small intestine, two feet from the stomach, showed intussusception. Spleen weighed 2,300 g, it was deeply congested and showed areas of haemorrhage and necrosis. Other organs were unremarkable on gross examination.

Histopathological findings

The interesting findings were present in micro sections of spleen, liver, lymph nodes and bone marrow. Splenic sinusoids were dilated and contained numerous small and large histiocytes, a few showed ingested red cells in the cytoplasm (Fig-1). The nuclear/cytoplasmic ratio was low and chromatin was mature. There were areas of haemorrhage and necrosis around periaarterial lymphoid sheath. Trabecular connective tissue was infiltrated with mononuclear cells. The architecture of the hepatic parenchyma was by and large maintained. Dense collection of lympho-histiocyte infiltrates were present in the portal tracts; a few containing ingested erythrocytes in the cytoplasm (Fig-2). Nuclei were vesicular, oval or indented in shape, and some of the nuclei were binucleate. Kupffer cells were prominent in the sinusoids and showed focal collection of histiocytes. Lymph nodes of hilar, me-

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Fig. 1: Splenic sinusoids showing numerous histiocytes with bland nuclei, a few containing ingested red cells in the cytoplasm (x 40)

Fig. 2: Dense infiltrate of mononuclear cells and histiocytes in the portal tracts along with a giant cell in the center. Binucleate histiocytes are also seen. (x 20)

diastinal and mesenteric groups were studied. The architecture of the lymph nodes showed loss of recognition of cortex and medullary zones with wide spread areas of non-suppurative necrosis and cellular depletion of lymphoid elements (Fig-3). The dilated sinusoids of lymph node were stuffed with numerous histiocytes, having abundant eosinophilic cytoplasm and few contained phagocytosed red cells (Fig-4). No granulomatous lesion was present. Bacterial, fungal and acid fast stains of spleen, lymph nodes and liver were negative. Bone marrow was partially autolysed, however, the hypercellularity could be appreciated. The precursors were not discernible, the histiocytes were observed morphologically but the ingested erythrocytes were less conspicuous. No viral inclusions were observed in any of the sections.

Discussion

VAHS is included in a group of disorders called haemophagocytic syndrome (HS), which is characterised by unifying features of a systemic proliferation of histiocytes of mononuclear phagocytes [1,2,6]. HS embraces familial haemophagocytic lympho-histiocytosis (FHL), an autosomal recessive disorder

Fig. 3: Lymph node showing wide spread area of non-suppurative necrosis and cellular depletion of lymphoid element (x 20)

Fig. 4: The dilated sinusoids of lymph node stuffed with numerous histiocytes, having abundant eosinophilic cytoplasm, and few containing phagocytosed red cells.

der and VAHS. It may involve lymph nodes, spleen, bone marrow, liver and even lepto-meninges [4]. The disease process is not limited to viral infections but may be triggered by variety of bacterial infections like tuberculosis, brucellosis, syphilis; parasitic like leishmaniasis [3,7]; fungal like candidiasis, histoplasmosis etc [8], and in association with malignant lesions, particularly lymphoblastic lymphoma [1]. The patients may have hereditary or acquired immune deficiency, which predisposes them to this entity [2-4]. A study of patients suffering from VAHS without any significant past history revealed evidence of acute immune deficit including striking lymphoid depletion of lymph node on subsequent investigations [5]. In a study conducted in Sweden [9], the workers felt that the association of VAHS with viral infections could be concomitant with onset of FHL, rather than a sole criterion to justify it as a separate entity. These cases were indistinguishable from FHL clinically, as well as by labora-

tory and histopathological methods [1].

The clinical presentations have been described in detail by Study group of the histiocyte society [2], however the abrupt onset, multi-system involvement with severe constitutional symptoms like high fever and pancytopenia are the commonest findings. High percentage of the patients have abnormality in coagulation system. It usually has a fulminant clinical course and high mortality. 6 out of 19 patients died in the original series studied by Risdall et al [5] and remaining gradually recovered. In studies conducted by other workers more or less similar observations have been made [3,5,7,9,11].

Microscopically, the active phase of the disease is preceded by infiltration of bone marrow by atypical lymphoid cells with areas of necrosis, depletion of haemopoietic cells and activation of histiocytes with haemophagocytosis. Granuloma may be noted. The end stage is usually marked with aplasia [10]. The diagnosis of VAHS is invariably so difficult that it is not always possible to establish the diagnosis when the patient is alive [9]. Clinical and histomorphological criteria, supported by viral studies are the final tools to establish the diagnosis. Langerhan's medullary reticulosis (previously called histiocytosis-X), where the main cells have cytologic features of Langerhan's cells, has been described to have more or less similar clinical findings and atypical histiocytes on histopathological examination [10,11]. Sinus histiocytosis and atypical reactive hyperplasia of reticuloendothelial system by infective agents may also mimic VAHS. At times, it has been misinterpreted as malignant histiocytosis (MH) due to multiorgan involvement and high mortality. The distinction between benign and malignant histiocytosis may be difficult at times, however, a low nuclear/cytoplasmic ratio, abundance of lightly stained cytoplasm, presence of large vacuoles of varying sizes and phagocytosed cells, favour benign lesion [1]. The nucleoli, if present are not prominent and mitotic figures are rare. Haemophagocytosis is uncommon in MH. Unfortunately, serological studies for viral etiology in patients of VAHS may not be reliable because of impaired immune response of the body.

Our patient manifested clinically as a case of viral fever with severe constitutional symptoms. On exami-

nation, marked hepatosplenomegaly and gradually progressive pancytopenia remained a matter of concern. In spite of all relevant investigations, the possibility of VAHS did not click. In a number of series most of the patients had similar nonspecific symptoms associated with fever and followed by hepatosplenomegaly, lymphadenopathy and pancytopenia [3-5,7].

To conclude, we presented a case of VAHS, in which in addition to wide spread proliferation of histiocytes, there was nonsuppurative necrosis of lymph nodes and spleen. These findings are consistent with the observations made by Reisman and Greco [1]. Though the clinical profile did not indicate the immune suppression but a similar episode, which occurred six months before this fatality, probably altered the immune response of the deceased towards the disease process.

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