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Unusual Causes of Haemophagocytic Syndrome

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Haemophagocytic syndrome is rare, often fatal clinical disorder in which release of inflammatory cytokines from macrophages results in marked haemophagocytosis. We are presenting two unusual cases of adults with haemophagocytic syndrome.

- **The first case is 30-year-old Saudi patient who had pulmonary tuberculosis associated with haemophagocytic syndrome.**
- **The second case is 34-year-old Sudanese woman who presented with multiple skin nodules and fever. Re-evaluation of her skin biopsy revealed panniculitic T-cell lymphoma.**

Mortality is reported to be high in both situations; however, these two cases were successfully treated and followed up for about 18 months. The treatment of haemophagocytic syndrome is directed at the underlying cause.

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Haemophagocytic lymphohistocytosis, also called "Haemophagocytic Syndrome" (HPS), is a reactive proliferative disorder that affects the antigen-processing macrophages which results in uncontrolled haemophagocytosis. Scott and Robb-Smith described this clinicopathological entity initially in 1939[1]. Rappaport in 1966 introduced the term malignant histocytosis (MH) to describe a similar entity with systemic proliferation of atypical neoplastic histiocytes[2]. Risdall et al in 1979 identified a benign generalized histiocytic proliferation different from MH with marked haemophagocytosis associated mostly with a systemic viral infection especially with Epstein Barr virus[3,4]. It was also shown, however, to be associated occasionally with non-viral infections, for example, Brucellosis, leishmaniasis, typhoid fever, Q fever, tuberculosis, gram-negative, gram positive bacteria and fungi. Malignant neoplasms, particularly malignant lymphoma, was recognized as a triggering cause of HPS[5]. The manifestations of the disorder are thought to be mediated by inflammatory cytokines, including interferon-gamma, (interferon γ), tumor necrosis factor (TNF), soluble interlukin-2 (IL-2) receptor, FAS ligand, granulocyte-monocyte colony-stimulating factor (GM-CSF), monocyte-colony-stimulating factor (M-CSF) and others[6]. Agents like Epstein-Barr virus activate T-lymphocytes resulting in cytokine release. Elevated levels of TNF-α, soluble IL-2 receptor, IL-1 and FAS Ligand are associated with the severity of the manifestations.

In this paper we report two cases of (HPS), one of them associated with TB, and the other with panniculitis- like T-cell lymphoma.

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THE CASES

Case 1

Thirty year old Saudi male patient was admitted to KAU hospital complaining of fever and fatigue for two months. The symptoms were associated with unmeasured weight loss. There were no night sweats, cough, jaundice, skin rash, abdominal pain, or change in bowel habits. The patient had no history of contact with a Tuberculosis patient, ingestion of raw milk, blood transfusion, recent travel or drug abuse. He was single with no history of extra marital sexual activity. He was a non-smoker, working as a clerk in a hospital.

On admission, he was pale with a fever of 38.5 ^{0}C; the remainder of the physical examination showed no abnormalities. Laboratory studies showed the following results: ESR 36mm/h, hemoglobin 7.8 g/dl, platelets 393 X 10^9 /L (393.000/mm^3), WBC 7 x 10^9/L (7.000/mm^3). The blood film showed hypochromic, microcytic red blood cells with leukoerythroblastic picture. No malarial parasites were identified on thick and thin blood film. Serum urea nitrogen, creatinine, liver enzymes and coagulation profile were all normal. HIV, EB virus, CMV, Herpes virus, parvovirus B19, and brucellosis were negative. Chest X-ray showed mediastinal lymphadenopathy with no parenchymal changes. CT scan of the chest revealed the same findings. In spite of negative cultures, ceftriaxone was administered as the patient appeared septic at admission. However, the patient discharged himself against medical advice. Ten days later, he returned to ER severely ill with fever, jaundice, and very dark colored urine. The patient was very pale with fever (39.8^{0}C). He was alert, and no cardiovascular or respiratory abnormalities or peripheral lymphadenopathy were detected. The liver was large at 4 cm below the right costal margin. Laboratory studies showed Hb 7.8g/dl, platelets 253 x 10^9/L (253.000/mm^3), WBC 12 x 10^9/L (12.000/mm^3). The blood film revealed the same findings. Urea, creatinine, lipid profile and electrolytes were normal.

Further laboratory studies disclosed the following values: AST 256 Iu/L NR (5-55); ALT 156 Iu/L NR (5-50); bilirubin 225 Umol/L NR (5-17); conjugated bilirubin 190 mol/LNR(2-7); LDH 713 u/L NR(100-225); prothrombin time: 20sec NR(10-16); partial thromboplastin time: 56sec NR(29-40) with low fibrinogen at 113 g/dl NR(180-350). Bone marrow aspirate cytology showed panhemophagocytosis by cytologically benign histocytes.

Biopsies of inferior mediastinal lymph node and lung revealed necrotizing granuloma, positive for acid-fast bacilli, diagnostic of TB. Due to liver derangement, the patient was started on modified doses of anti-TB medications. He responded very well to anti-TB treatment and was discharged in good general condition, with a remarkable improvement during follow-up. The most recent complete blood count parameter showed hemoglobin of 12.5 g/dL, white blood cells of 8 x 10^9/L (8.000mm^3) with normal differential and platelets count of 350 x 10^9 /l (350.000/mm^3).

Case 2

Thirty-four year old Sudanese female was admitted to KAU hospital presented with intermittent high fever, anorexia, weight loss and multiple nodular swelling over her entire body for four months duration.

The fever was not associated with rigors or sweating. She gave a history of recurrent malaria in the past; no other history was of significance. Physical examination revealed fever of 38-40^{0}C, weight loss, severe palor, malaise, weakness and multiple nodular swelling from 2 to 5 cm in diameter, non tender and red distributed all over her body. She had an ejection systolic murmur at aortic valve with radiation to the apex. Abdominal examination revealed hepatomegaly 6 cm below the right costal margin and a just palpable spleen. There was no lymphadenopathy. Central nervous system

examination was normal. Fundal examination showed 2 roth spots in the right eye. During her stay in hospital, the patient developed progressive jaundice and her liver enlarged to 16 cm below the costal margin. There was no palpable lymphadenopathy no increase in the spleen size.

Laboratory studies showed low hemoglobin 8.7 g/dL, platelets 192 x 10^9/L (192.000/mm^3), and white blood cells 2 x 10^2 (2.000mm^3). Her hemoglobin dropped after two days to 5.9 g/dL with 16% reticulocytes, peripheral blood film revealed pictures of hemolysis, with no malaria parasites nor atypical cells seen. Comb's test was positive for IgG antibodies; urea and creatinine were normal. On admission, liver function tests showed normal alkaline phosphatase but during hospitalization, alkaline phosphatase increased to 267 Iu/L NR (35-105). Parenchymal liver enzymes also increased to 6 times with total bilirubin of 193 Umol/L and LDH 1065 Iu/L. Antinuclear antibody, double stranded; DNA, rheumatoid factor, hepatitis B and C profile, HIV, and Brucella cultures were all negative. Her PT and PTT were prolonged (PT:18 sec), (PTT: 50 sec) Chest x-ray and ECG showed no abnormalities. Ultrasound of the abdomen revealed hepatosplenomegaly with no lymphadenopathy. Bone marrow study showed active bone marrow with no evidence of infiltration by malignancy. Skin biopsy was performed which showed features consistent with panniculitis. The patient's condition worsened with progressive deterioration in her liver enzymes; therefore, steroids were started empirically. She responded dramatically to the steroids, became afebrile and stopped hemolysing. Her jaundice improved and the skin nodules regressed in size. The exact etiology of her panniculitis had not been determined at that time. She was feeling well for about seven months, after which fever reappeared for which there was no obvious cause.

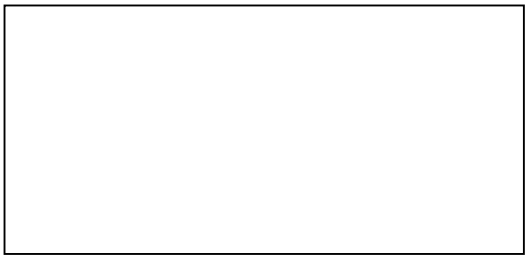

Figure 1.The neoplastic cells infiltrate around Fat cells in a lace-like pattern (H & E stain 250 x magnification)

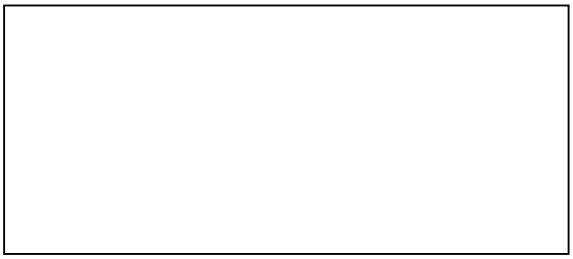

Figure 2. The neoplastic cells are strongly positive with T-cell marker (UCHL-1) marker CD45RO (immunohistochemical stain 400 x magnification)

Physical examination showed several scars of her healed panniculitic lesions and no new lesions. Secondary to steroids, her face became cushingoid with malar flush. Hepatomegaly was 12 cm below the costal margin (better than before), and the remainder of the physical examination showed no abnormalities.

Re-investigations revealed the following abnormal results: Hb 8.4 g/dL, total white blood cell count of 2 x 10^9 /L (2.000 mm^3), platelets 120 x 10^9 /L (120.000 mm^3), ESR 20 mm/hour, liver enzymes raised three times the normal level, LDH 1205 u/l NR (240-480). Bone marrow aspiration cytology showed increased cellularity with panhemophagocytosis and large scattered atypical lymphocytes. Bone marrow biopsy revealed normocellular bone marrow with presence of all three haematopoietic cell lines. Scattered foamy histiocytes were seen. Review of the previous skin biopsy showed a subcutaneous mononuclear lymphoid cell infiltrate, and occasional plasma cells and histiocytes. The majority of the lymphoid cells were small, although, occasional large ones were seen. They exhibited elongated irregular convoluted hyperchromatic nuclei. These lymphoid cells were seen in nodular formation as well as perculating around fat cells without destroying them (lace like pattern). Mitoses were prominent in addition to atypical forms. These tumor cells were strongly positive for LCA, CD45Ro, CD5, CD3, (T-cell markers) and negative with (CD45A, CD20, CD79 (B cell markers). Karyorrhexis was prominent, dermal infiltration was present and areas of subcutaneous

fat necrosis were identified. There was no angiocentric or destructive pattern of these atypical lymphoid cells. The skin biopsy's revised diagnosis was subcutaneous panniculitic T-cell lymphoma. Subsequent liver biopsy showed fatty change of moderate degree in addition to extramedullary hematopoiesis. Eight months later after receiving chemotherapy, bone marrow trephine biopsy revealed normocellular bone marrow with mild degree of fibrosis.

DISCUSSION

Histiocytic proliferation with haemophagocytosis is a rare condition; however, it is often fatal. It is divided into different clinical categories consisting of: (i) a sporadic disorder; (ii) a form associated with acute infection (usually viral); (iii) a familial form seen in children; and (iv) a form associated with malignant disorders, immunodeficiencies or defective leukocyte functions[4].

The pathogenesis of this syndrome is related to uncontrolled activation of the cellular immune system, which results in excessive hemophagocytosis with the release of inflammatory cytokines. Natural killer cell function impairment is postulated as a mechanisn in familial hemophagocytic syndrome. Moreover, in T-cell lymphoma, HPS is thought to be triggered by a phagocytosis inducing-factor secreted by neoplastic T cells[7].

The first patient we described had a haemophagocytic histiocytosis associated with tuberculous infection (no evidence of viral infection by serology). At least a dozen cases of tuberculosis associated with HPS have been reported[8,9]. The majority of patients were either immunosuppressed or presented with miliary tuberculosis. In spite of the high incidence of tuberculosis in Saudi Arabia (16.04/100,000) the association with HPS appears to be exceedingly rare[10]. TB frequently presents with fever, weakness, weight loss, hepatosplenomegaly and laboratory features such as anemia, leukopenia monocytosis, basophilia, disseminated intra vascular coagulation and rarely pancytopenia[11]. The exact mechanism and pathogenesis of this unusual manifestation in association with TB is not clear. Perhaps the immunologic status of these patients is a determining factor. Moreover, it may occur either due to primary alteration in the phagocytic cells or in the ingested elements. It is not clear whether tuberculosis bacilli directly alter histiocytic reactions or if other mediators from tuberculosis bacilli are associated with haemophagocytosis[8]. Infection associated HPS, although potentially a reversible condition is noted to have a high mortality of about 30-40%[12]. Tuberculosis associated with HPS carries a higher mortality that was observed in most cases that had post-mortem bone marrow biopsy. In our case the anti-tuberculosis therapy achieved a clinical and laboratory cure.

Subcutaneous panniculitic T-cell lymphoma (SPTCL) is a rare disease with fewer than 50 cases reported in the literature[13]. It was originally described by Gonzales et al, as a subset of post-thymic T-cell lymphoma involving the subcutis. Panniculitic-T-cell lymphoma has been included as a provisional clinicopathologic entity in the revised European – American lymphoma classification (REAL) and the European Organization for Research and Treatment of Cancer (EORTC) classification for primary cutaneous lymphoma. The WHO classification of haematological malignancies accepted it as a distinct clinicopathological entity. SPTCL average age is 46 years, and women are more frequently affected than men[14,15].

SPTCL usually presents with multiple tan-to-red, subcutaneous non-tender tumors or plaques from 0.5-13 cm in diameter, most frequently involving the extremities and trunks with constitutional symptoms that include fever, loss of body weight, malaise, fatigue, myalgia, chills and weight loss. Systemic HPS frequently occurs, accounting for many of the constitutional symptoms and the cause of death in the majority of patients[14]. This syndrome is probably the result of macrophage activation by cytokines produced by the neoplastic T cells, and is due to phagocytosis of blood cells by non-neoplastic macrophages in the bone marrow, spleen, liver and lymph nodes[16]. A well-known cause

of both disordered T-cell response and haemophagocytic syndromes is Epstein Barr virus infection[17]. Only a few cases of SPTCL have been examined for EBV but the majority of these cases were positive[17]. SPTCL is widely regarded as a tumor of cytotoxic T-cells, it shows positive expression of CD4, CD8, and absence of CD5[14]. CD7 has been reported sporadically; and some cases express γδT-cell receptors (TCR)[18,19].

Treatment that has been used in the past include systemic chemotherapy, radiotherapy and high dose chemotherapy with stem cell support. McGinnis KS et al recently described DeniLeukin diftitox, which is a recombinant fusion protein that combines human interleukin 2 and diphtheria toxin as an effective, relatively non-toxic therapy for panniculitic T-cell lymphoma[20]. Our patient received CHOP (Cyclophosphamide, Doxorubcin, Vincristine and Prednisolone). A total of 8 courses were administered; and control of HPS and remission was achieved with this treatment. Two years after completion of chemotherapy, there was no evidence of disease recurrence.

CONCLUSION

We present two uncommon cases where tuberculosis and subcutaneous panniculitic T-cell lymphoma were the causes of haemophagocytosis. We emphasize the importance of searching for tuberculosis in a patient with fever of unknown origin and haemophagocytosis especially in our part of the world where TB is very common. In addition, we stress the importance of diagnostic survey to rule out T-cell lyphoma in patients with Panniculitis and HPS. Moreover, HPS should be considered in patients with malignancies or chronic infections who have additional unexplainable symptoms including pancytopenia - as both diseases follow an accelerated and possibly fatal course. It is imperative that an early diagnosis is made and appropriate therapy promptly initiated.

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