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Hemophagocytic Syndrome Associated with Bilateral Adrenal Gland Tuberculosis

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We report a case of a patient who presented with hemophagocytic syndrome (HPS) and adrenal crisis associated with bilateral adrenal gland tuberculosis, and resulted in a poor outcome. A 50-year-old man was transferred to our hospital from a local clinic due to fever, weight loss, and bilateral adrenal masses. Laboratory findings showed leukopenia, mild anemia, and elevated lactate dehydrogenase. Computed tomography (CT) of the abdomen revealed bilateral adrenal masses and hepatosplenomegaly. CT-guided adrenal gland biopsy showed numerous epithelioid cells and infiltration with caseous necrosis consistent with tuberculosis. Bone marrow aspiration and biopsy showed significant hemophagocytosis without evidence of malignancy, hence HPS associated with bilateral adrenal tuberculosis was diagnosed. During anti-tuberculosis treatment the patient showed recurrent hypoglycemia and hypotension. Rapid ACTH stimulation test revealed adrenal insufficiency, and we added corticosteroid treatment. But pancytopenia, especially thrombocytopenia, persisted and repeated bone marrow aspiration showed continued hemophagocytosis. On treatment day 41 multiple organ failure occurred in the patient during anti-tuberculous treatment and steroid replacement.

Key Words : Histiocytosis, Tuberculosis, Adrenal glands

INTRODUCTION

Hemophagocytic syndrome (HPS) is an unusual disorder characterized by a benign proliferation of mature histiocytes and an uncontrolled phagocytosis of some hematic precursors in the bone marrow. Known causes of HPS include infections, tumors, drugs, autoimmune diseases, and other immunosuppressive states[1]. Various infections can activate macrophages or T-cells, and the overproduction of proinflammatory cytokines by these cells are thought to be important in monocyte/macrophage activation[2]. Hypercytokinemia by these cells is important in the pathogenesis of HPS[3]. Known infectious agents that are associated with HPS include Epstein-Barr virus[4], cytomegalovirus[5], tuberculosis[6, 7], herpes simplex virus 6[8], human immunodeficiency virus[9], and leshimania[10]. However, there are no case reports described HPS associated with bilateral adrenal gland tuberculosis with combined adrenal crisis. We report the case of a patient who presented with HPS associated with bilateral adrenal gland tuberculosis.

CASE REPORT

A 50-year-old man was transferred to our hospital from a local clinic due to fever and weight loss. The patient had been healthy until 15 days prior to his admission, when, at that time, he began to feel febrile, lost his sense of taste, and developed a poor appetite. The symptoms continued until the admission. Upon examination at the originating clinic, adrenal masses had been found on CT. On admission the patient's temperature was 37.7℃, pulse 80 beats/min, respiration rate 20 breaths/min, and blood pressure 120/80 mmHg. On examination, the patient appeared ill and prostrated. Liver was palpable in 1 finger-breadth on the epigastric area and a 1.5x1.0 cm sized firm and nontender right supraclavicular lymph node was palpated, but otherwise unremarkable. His leukocyte count was 1,700/μL with

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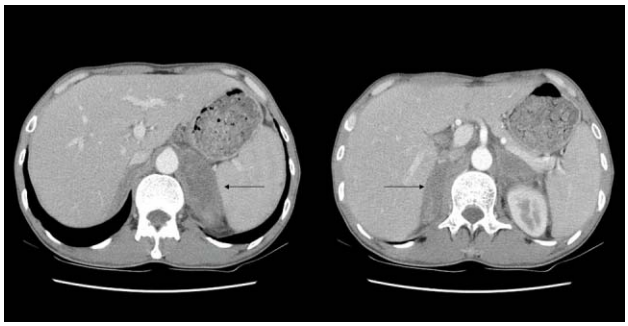

Figure 1. CT of abdomen revealed bilateral adrenal masses with central necrosis.

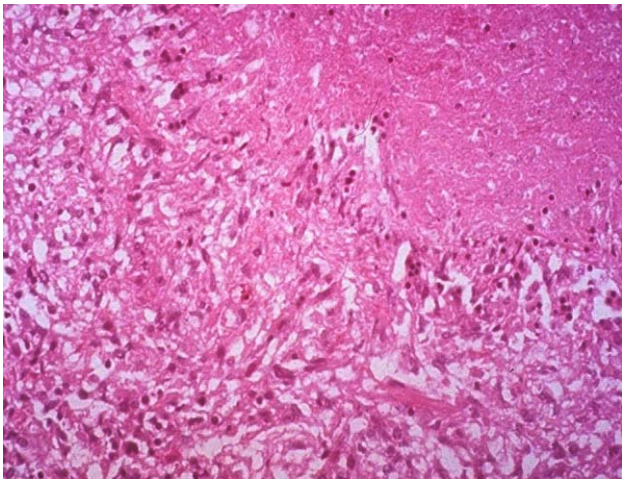

Figure 2. CT-guided adrenal gland biopsy shows numerous epithelioid cells and caseous necrosis consistent with tuberculosis.

65% neutrophils, hemoglobin 10.6 g/dL, and platelet 142,000/L. His blood chemistry revealed total serum protein was 6.3 g/dL, albumin 3.6 g/dL, aspartate transaminase 52 IU/L, alanine transaminase 29 IU/L, alkaline phosphatase 183 IU/L, sodium 129 mmol/L, potassium 4.0 mmol/L, lactate dehydrogenase (LDH) 1415 IU/L, and serum ferritin >2000 ng/mL. The renal function was normal. Cortisol in the morning and evening was 17.8/20 μg/dL (normal range: 5～25 μg/dL) and ACTH in the morning and evening 726/265 pg/dL (normal range: 10-56.7 pg/dL). Serologic test for Epstein-Barr virus and cytomegalovirus were normal. Chest radiographs obtained on admission revealed normal findings, but a CT scan of the abdomen revealed bilateral adrenal masses and hepatosplenomegaly (Figure 1). Right adrenal mass measured 6x1.7 cm and the left was 8x3 cm in size. CT-guided adrenal gland biopsy was done and showed numerous epithelioid cells and caseous necrosis consistent with tuberculosis (Figure 2). But, an AFB stain of the tissue and polymerase chain reaction for *Mycobacterium tuberculosis* were negative. On subsequent bone marrow aspiration and biopsy, hemophagocytic histiocytes had increased in proportion (4.6%) without accompanying evidence of malignancy (Figure 3), hence HPS associated with adrenal gland tuberculosis was diagnosed. Biopsy of the supraclavicular lymph node revealed necrosis, but no evidence of malignancy. Treatment with isoniazid, rifampin, ethambutol, and pyrazinamide was started immediately. On treatment day 4, the patient developed jaundice and elevated levels of transaminases. We discontinued hepatotoxic drugs (isoniazid, rifampin, pyrazinamide, and acetaminophen) and changed his medications to ethambutol, cycloserine, streptomycin, and ciprofloxacin. During the anti-tuberculous treatment the patient showed recurrent hypoglycemia and hypotension. Rapid ACTH stimulation test revealed adrenal insufficiency. Corticosteroid treatment was added. After supplementation with corticosteroid, the hypotension and hypoglycemia were corrected. After normalization of liver function, isoniazid was restarted with a gradual increase in dose. But pancytopenia progressed during the anti-tuberculous treatment. On treatment day 30, repeated bone marrow aspiration was performed and showed that numerous hemophagocytic histiocytes persisted (5.0%). On treatment day 41, the patient expired due to multiple organ failure (including disseminated intravascular coagulation, hepatic failure, and renal failure).

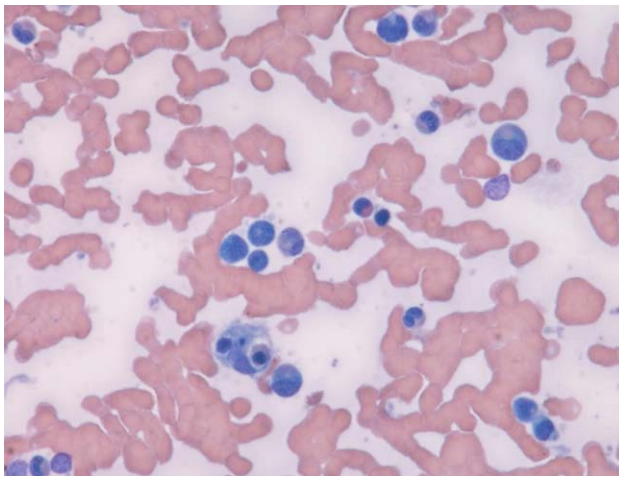

Figure 3. On bone marrow aspiration, mature histiocyte engulfing hematic cells is seen observed (5.0%).

DISCUSSION

HPS is clinically characterized by fever, hepatosplenomegaly, pancytopenia (and associated complications, such as spontaneous bleeding or infection), coagulation disorders, and biochemical disturbances, such as hyperferritinemia, and elevated triglyceride and lactate dehydrogenase levels[11]. Risdall et al in 1979

described infection-associated HPS as a benign generalized histiocytic proliferation with marked hemophagocytosis associated with systemic viral infection[12]. Tuberculosis is a nonviral infection that can cause HPS, but only several cases have been reported[6, 7]. Most of these patients had underlying disorders, such as chronic renal failure[13], cancer[14], diabetes[15], and acquired immunodeficiency syndrome[9], and their outcomes were poor. A relationship has been implied between systemic histiocytic proliferation and an underlying immunocompromised state, suggesting that immunologic disturbances occurring in infections could play a role in the pathogenesis of HPS[16].

The mechanism by which tuberculosis causes HPS is not known, but there are several possible explanations. Phagocytosis of mycobacteria by macrophages is the initial immune response to tuberculous infection. Some bacilli are killed within the macrophages, but others survive and replicate within their cellular hosts. In either case phagocytosis leads to cytokine production by the macrophages. Release of tumor necrosis factor (TNF)-α, interleukin (IL)-12, and other chemotactic cytokines perpetuates the host immune response and leads to the recruitment of lymphocytes, neutrophils, and monocytes. TNF-α leads to the fever and tissue wasting seen with both tuberculosis and hemophagocytic syndrome[17]. This cytokine, in conjunction with IL-12 and IL-5, leads to the migration of monocytes and macrophages to regional lymph nodes. This allows for the expansion of antigen-specific T cells, which in turn may lead to a secondary release of cytokines and increased proliferation and activation of phagocytes[7, 18]. This process is presumably magnified in the setting of impaired cell-mediated immunity, which explains the increased prevalence of infection-associated HPS in patients with HIV infection and other forms of immunosuppression[9].

Because HPS is rare, no controlled clinical trials of therapy have been performed. For patients with HPS associated with pathogens other than Epstein-Barr virus, supportive care and treatment of the underlying infection is associated with recovery in 60~70%. Among adults with HPS, age>30 years appears to be associated with an increased risk for death[19].

In this case, on admission the patient had a subclinical adrenal insufficiency due to a reduction in the functioning adrenal tissues. In an adrenal function test, the cortisol level was within the normal range, but the ACTH (adrenocorticotropin) level was elevated highly. Because of the high possibility of adrenal crisis, early corticosteroid replacement was more reasonable than replacement after symptoms occurred. Ineffective control of HPS and tuberculosis by second line anti-tuberculous treatment might have allowed pancytopenia to persist for a longer duration, and might have contributed to hypercytokinemia and multiple organ failure. Because hypercytokinemia is the main pathophysiology of HPS, a cytokine reducing regimen may be essential in the acute phase. Several papers described the successful treatment of HPS using plasmapheresis[20, 21]. Our patient's condition was refractory to corticosteroid and anti-tuberculous treatment. In such a refractory case, plasmapheresis may be considered to reduce cytokine and possibly improve the patient's clinical status in the acute phase.

HPS associated with tuberculosis is a very rare disease and may resolve concurrent with tuberculosis treatment. However, early recognition and treatment are needed because of the possibility of a poor outcome.

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