Hemophagocytic Syndrome Associated with Diffuse Large B-Cell Lymphoma: A Case Report

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A 54-year-old woman was admitted to Chi-Mei Foundation Hospital because of fever, chills and left lower chest pain. The laboratory findings revealed bicytopenia (anemia and thrombocytopenia), an abnormal liver profile, and elevated blood levels of C-reactive protein, ferritin and triglyceride. She was endotracheally intubated and received mechanical ventilation due to respiratory distress. Hepatosplenomegaly was found in her abdominal computed tomographic scan. Bone marrow biopsy revealed active hemophagocytosis. Because of the prolonged febrile state, a gallium scan was performed, which revealed neck and mediastinal lymphadenopathy. The neck lymph node biopsy was proven to be diffuse large B-cell lymphoma (DLBCL). A diagnosis of DLBCL associated with hemophagocytic syndrome (HPS) was made. However, uncontrolled sepsis developed after chemotherapy with cyclophosphamide, oncovorin, and dexamethasone, and the patient died. DLBCL associated with HPS is rare and has been effectively treated with chemotherapy in some reports. The safety of chemotherapy for DLBCL-related HPS has never been reported in critically ill patients with mechanical ventilation, and the prognosis is extremely poor. ***(Thorac Med 2008; 23: 55-60)***

Key words: Hemophagocytic syndrome, diffuse large B-cell lymphoma

Introduction

Hemophagocytic syndrome (HPS) is the phenomenon in which activated macrophages phagocytize red blood cells, white blood cells, and platelets. It is characterized by febrile pancytopenia, jaundice, hepatosplenomegaly, and hemophagocytosis in the bone marrow, liver, or lymph nodes [1]. A variety of infectious diseases, including viral, bacterial, fungal, and parasitic infections [2-4], collagen-vascular diseases, and malignancies, are associated with HPS. HPS has also been associated with almost all T-cell lymphomas [5-7]; this phenomenon is less common in B-cell lymphomas. In this study, we report a diffuse large B-cell lymphoma associated with reactive hemophagocytosis.

Case Report

A 54-year-old woman was admitted to Chi-Mei Foundation Hospital because of fever, chills

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and left lower chest pain. The laboratory findings on admission revealed bicytopenia (hemoglobin 6.9 g/dl, platelets 43,000/mL), a higher C-reactive protein level (358 mg/L), and an abnormal liver profile (aspartate aminotransferase 105 U/L, alanine aminotransferase 20 U/L, gamma-glutamyl transferase 210 U/L, total bilirubin 7.09 mg/dL, direct bilirubin 6.57 mg/dL). She was endotracheally intubated and mechanically ventilated because of acute respiratory failure. Due to a suspicion of intraabdominal infection, an abdominal computed tomographic (CT) scan was done, which depicted only hepatosplenomegaly. There was no intraabdominal abscess, and no biliary stones. She was treated with antibiotics after blood, sputum, and urine cultures were obtained.

A hematologist was consulted. The blood sample was drawn, and hyperferritinemia (> 2,000 ng/ml) and hypertriglyceridemia (241 mg/dL) were noted. A bone marrow examination from the iliac crest was performed, and the specimens revealed activated histiocytes phagocytizing red blood cells, consistent with hemophagocytic syndrome (Figure 1). A gallium scan revealed multiple neck and mediastinal lymphadenopathies (Figure 2). The chest CT also confirmed the existence of numerous lymphadenopathies at the bilateral neck (Figure 3), supraclavicular region, bilateral axilla, mediastinum, and retroperitoneum.

On physical examination, palpable stony hard lymph nodes around the bilateral supraclavicular fossa and neck were found. After percutaneous lymphadectomy, biopsy showed diffused lymphoid infiltrates with infarction and coagulative necrosis. Immunohistochemically, these atypical lymphocytes expressed CD20 (Figure 4), Bcl-2, Bcl-6, MUM-1, and IgM without CD3, CD10, CD30, IgD, HHV-8-LANA, and EBV-LMP-1.

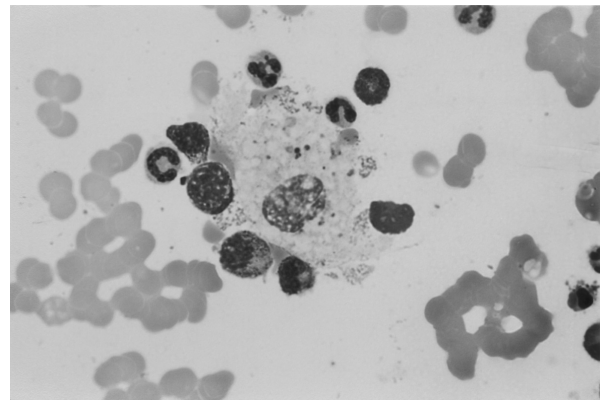

Fig. 1. Three red blood cells in the cytoplasm and 2 attached to the membrane of the activated histiocyte, consistent with hemophagocytosis, found in the iliac crest marrow biopsy (original magnification x 1000).

The CD21 staining highlighted focal residual follicular dendritic meshworks. The proliferation fraction as determined by Ki-67 was high at 90%. A diagnosis of diffuse large B-cell lymphoma (DLBCL) associated with hemophagocytic syndrome (HPS) was made.

The oncologists suggested cyclophosphamide, oncovorin, and dexamethasone as chemotherapy agents. After receiving chemotherapy, pancytopenia developed (leukocyte count 200/mL with an absolute granulocyte count of 168/mL, hemoglobin 5.3 g/dL, and platelet count of 5000/mL). Her later hospitalization course was complicated by refractory metabolic acidosis (pH 7.318, pCO2 23.9 mmHg, HCO3 12.0 mmHg, base excess -12.0 mmHg), and acute renal failure (creatinine 3.3 mg/dL, compared with the previous level of 0.6 mg/dL within 10 days). The patient died of uncontrolled sepsis after futile antibiotics therapy.

Discussion

HPS is associated with various conditions, such as viral, bacterial, fungal, and parasitic infec-

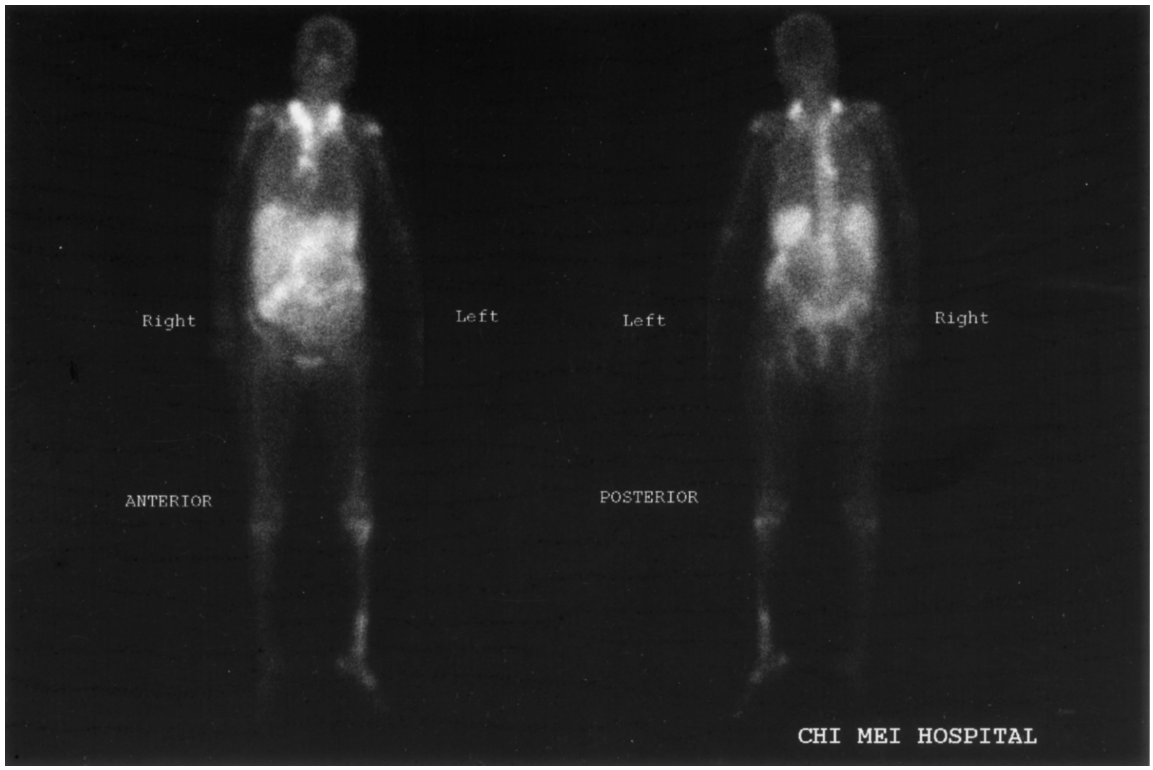

Fig. 2. Gallium scan showing multiple neck and mediastinal lymphadenopathy.

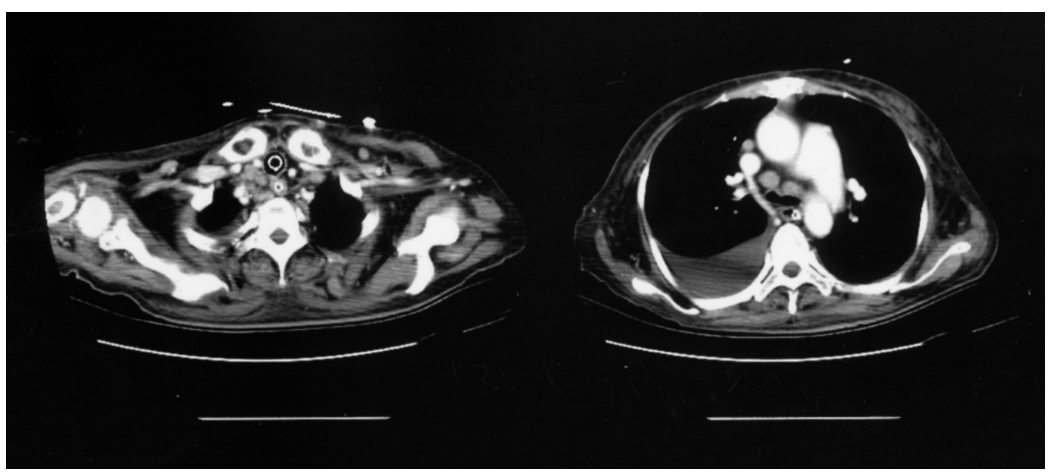

Fig. 3. Numerous lymphadenopathies at the bilateral neck and subcarinal area, found in the chest CT.

tious diseases [2-4], collagen-vascular diseases, and hemato-oncologic cancers. An analysis of 23 patients with HPS in Taiwan disclosed that most HPS cases are related to hematologic malignancies, including non-Hodgkin's lymphomas, leukemia, and myelodysplastic syndromes. Non-Hodgkin's lymphomas were the major cause, and only 2 B-cell lymphomas were found in an etiology study [7]. A series with a small number of cases in 1975 also confirmed T-lymphoma

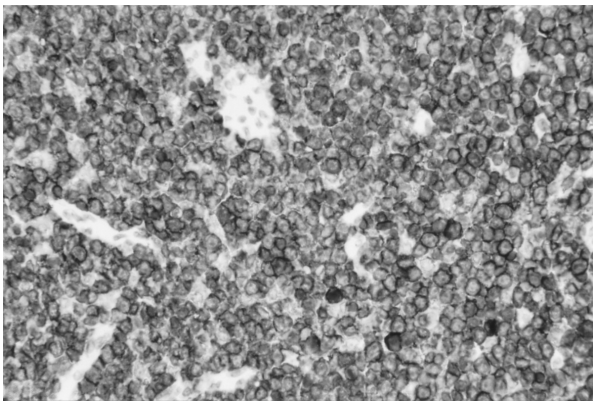

Fig. 4. Atypical lymphocytes expressing CD20 immunohistochemically (original magnification x 400).

predominance [5]. HPS was once considered only to be associated with T-cell type lymphomas and in all types of histology [5-7]. HPS does occur in B-cell lymphoma, though much less commonly, and when it does, it is called B-cell lymphoma-associated HPS (BCL-HPS).

BCL-HPS has several special clinical features. It is most often reported in Japanese populations in the medical literature [8], and even though lymphoma resulting in hemophagocytosis has T-lymphoma predominance, the predominance is not observed in Japanese populations [9]. Murase *et al*. proposed an Asian variant of intravascular lymphomatosis, called malignant histiocytosis-like B-cell lymphoma [10]. The cause of the racial difference remains unclear, and requires further investigation.

In a reassessment of previously reported cases in 1975, Wilson reported the earliest BCL-HPS [5]. However, the paper does not describe which histology of B-cell lymphoma caused HPS. In 1992, Barberan reported a fulminant and rapidly fatal case of HPS related to kappa-monoclonal B immunoblastic lymphoma [11]. Other case reports include T-cell-rich B-cell lymphoma [12], angiotropic B-cell lymphoma [13], and diffuse large B-cell lymphoma [14-15]. All these patients had a fulminant course, complicated by febrile pancytopenia, and died of severe sepsis [11-15].

The most common manifestations of lymphoma-related HPS are swinging fever and peripheral blood cytopenia [16]. Peripheral lymphadenopathy is not always found in these cases. The absence of peripheral lympadenopathy makes the diagnosis of BCL-HPS difficult, especially if there are no bone marrow infiltrations [17]. Since BCL-HPS is characterized by a fulminant course and rapid fatality, the patients affected by BCL-HPS are diagnosed after autopsy [11-14].

In general, HPS is considered to be a cytokine dysregulation resulting in histiocyte activation. Non-specific management for HPS is immunosuppressive drugs with methylprednisolone or cytotoxic agents such as cyclosporine. Because different diseases cause HPS, the underlying conditions should be considered to begin definite therapy. If the HPS is caused by infection, adequate anti-microbial agents are considered reasonable [2-4]. Any administration of immunosuppressive or cytotoxic agents is contraindicated in these conditions. In collagen-vascular disease-related HPS, for example systemic lupus erythematosus, methylprednisolone alone or with intravenous immunoglobulin is effective in some cases [18]. The therapy should be started after a detailed etiology workup, if possible, and aimed toward treating the underlying disease, in order to achieving the best outcome.

Chemotherapy is effective in controlling lymphoma. For BCL-HPS, chemotherapeutic agents with cyclophosphamide, adriamycin, vincristine, and prednisolone (CHOP) were the acceptable regimen in previous reports [15, 19-20], and achieved a successful resolution in 1 patient [15]. However, another case report showed a higher recurrence rate of B-cell lymphoma after chemotherapy, even during the interval after chemo-

therapy [19].

Our patient was admitted because of pancytopenic fever. Although HPS was diagnosed after serial blood biochemistry workup, the underlying disease itself was diagnosed after the presence of a neck lymph node. Because of the diagnostic difficulty reported previously, BCL-HPS should be considered, and a whole body gallium scan is indicated due to the possibility of the absence of a peripheral lymph node. However, with an acceptable CHOP regimen for the condition, the prognosis remained unclear. In patients with mechanical ventilation, the outcome is extremely poor.

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瀰漫性大 B 細胞淋巴瘤引起的嗜血症候群：病例報告

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一名 54 歲女性因為發燒、寒顫以及左下胸痛而住院。實驗室檢查顯示紅血球以及血小板兩種血球減少、不正常的肝指數、以及升高的 C 反應蛋白、血中儲鐵蛋白和三酸甘油脂。因為呼吸困難，病人在插入氣管內管後接受機器通氣治療。她的腹部電腦斷層顯示肝脾腫大，骨髓穿刺切片顯現活動中的血細胞吞噬情形。因為持續的發燒，在接受鎵 67 造影掃描後顯示明顯變大的頸部和縱膈淋巴結，頸部淋巴結組織切片證實為瀰漫性大 B 細胞淋巴瘤，病人因此診斷瀰漫性大 B 細胞淋巴瘤引起的嗜血症候群。在接受 cyclophosphamide 、 oncovirin 、和 dexamethasone 為主的化學治療後，病人出現無法控制的敗血症而死亡。由 B 細胞淋巴瘤造成的嗜血症候群是十分罕見的；此外，雖然某些個案報告提出嗜血症候群可以使用化學治療來有效控制，但對於接受機器通氣之重症病人的化學治療安全性從來沒有被提出來過。基于本病例個案，我們認為在機器通氣的重症病人使用化學治療來控制瀰漫性大 B 細胞淋巴瘤引起的嗜血症候群的預後是不佳的。*(胸腔醫學* ***2008; 23: 55-60****)*

關鍵詞：嗜血症候群，瀰漫性大 B 細胞淋巴瘤

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