

Case Study

# Primary Mediastinal Non-seminomatous Germ Cell Tumor Associated with Hemophagocytic Syndrome

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A 20-year-old man with a primary non-seminomatous mediastinal germ cell tumor (yolk sac tumor and immature teratoma) developed hemophagocytic syndrome (HPS) three months after surgical resection. Around the same time, the patient was found to have bone metastases of the germ cell tumor. No other hereditary or acquired diseases related to HPS were found. The thrombocytopenia was refractory to corticosteroid therapy but improved after chemotherapy performed for germ cell tumor progression. Only three cases of germ cell tumor associated with reactive hemophagocytosis have been previously reported. Successful treatment of the present case by chemotherapy for HPS suggests a close relationship between this rare complication and germ cell tumor. [*J Clin Exp Hematopathol* 49(2) : 117-120, 2009]

**Keywords:** germ cell tumor, hemophagocytic syndrome

## INTRODUCTION

In general, germ cell tumors are sensitive to chemotherapy and have a relatively favorable prognosis. However, primary mediastinal non-seminomatous germ cell tumor has very poor prognostic features, and it has been classified in the poor risk group in the International Germ Cell Cancer Collaborative Group, whether or not metastases are present.<sup>1</sup> The 5-year overall survival rate is approximately 50% for patients treated with the standard BEP (bleomycin, etoposide, and cisplatin) regimen.<sup>2</sup> Many clinical trials of high-dose chemotherapy with autologous stem cell support have been performed to identify a protocol that would improve the outcome of these patients.

Hemophagocytic syndrome (HPS) is characterized by fever, pancytopenia, liver dysfunction, and hemophagocytosis in the bone marrow. Hypercytokinemia induced by activated T lymphocytes and macrophages plays an important role in the pathogenesis of HPS.<sup>3</sup> HPS is divided into two types: the primary familial type and the secondary type. The secondary type is often associated with infection, autoimmune dis-

eases, and malignancies.

The case of a 20-year-old man with primary mediastinal non-seminomatous germ cell tumor who developed HPS three months after surgical resection is presented. The thrombocytopenia caused by the hemophagocytosis was refractory to corticosteroid therapy but improved after chemotherapy for progression of the germ cell tumor. This patient's clinical course suggests a close relationship between HPS and germ cell tumor.

## CASE REPORT

A 20-year-old man complained of chest pain in May 2006. Chest computed tomography (CT) revealed an anterior mediastinal solid tumor with a maximal diameter of 6.5 cm (Fig. 1A). Surgical resection was performed, and pathological examination showed proliferation of atypical cells with prominent nucleoli. Schiller-Duval bodies, which are glomerulus-like structures with a central blood vessel surrounded by tumor cells, and immature neural tissue and skeletal muscle with stromal tissue were also noted in the specimen (Fig. 1B, 1C). The patient was diagnosed as having a mediastinal germ cell tumor, a mixed type of yolk sac tumor and immature teratoma. From mid-June, one month after surgery, the patient developed a recurrent fever. Elevated levels of serum aspartate aminotransferase (AST, 68 IU/L) and alanine aminotransferase (ALT, 151 IU/L) were documented, and they increased to 402 IU/L and 474 IU/L, respectively, at the beginning of August. The serum total bilirubin also increased to 6.67 mg/dL. Hepatitis B virus surface antigen and anti-

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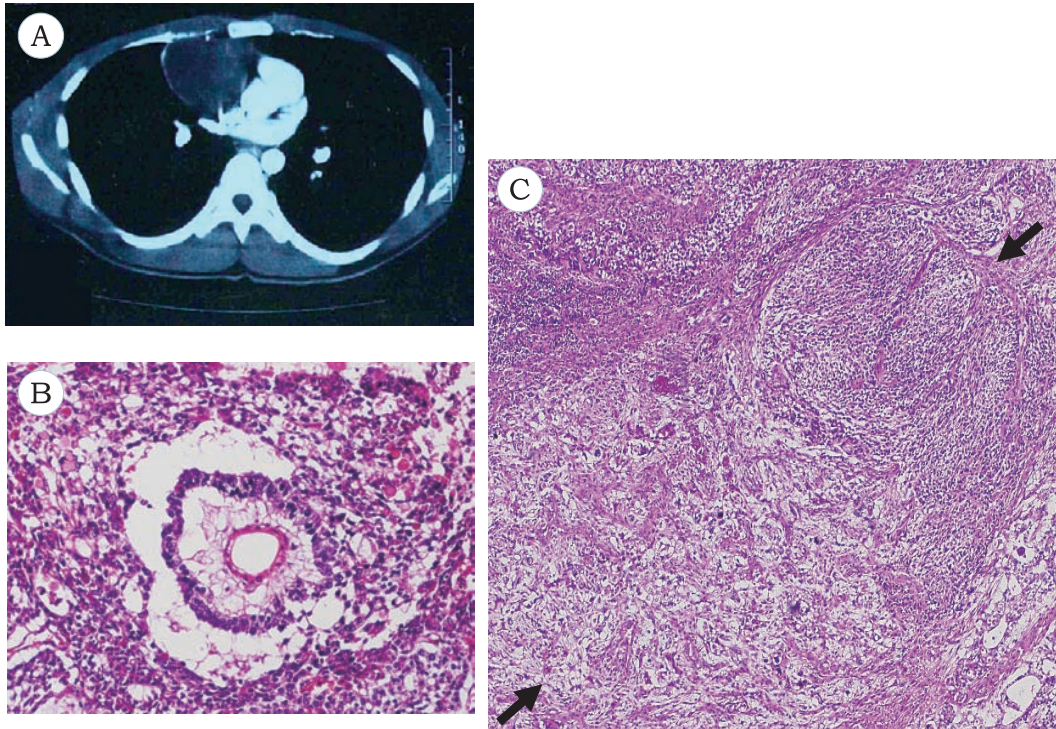
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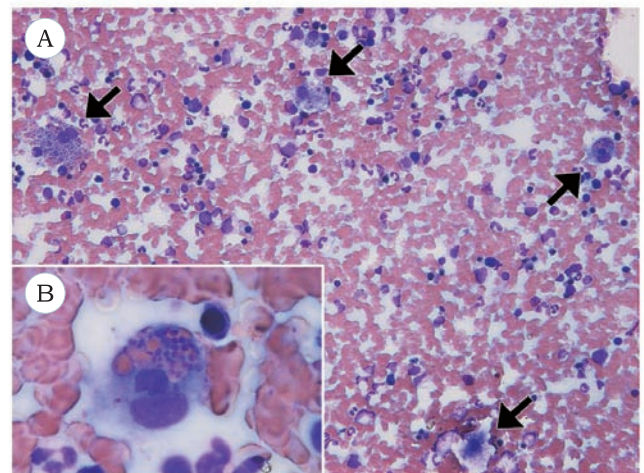
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**Fig. 1.** Computed tomography and histological examination. (*1A*) Chest computed tomography. A large mass in the anterior mediastinum is noted. (*1B, 1C*) Resected mediastinal mass specimen. Schiller-Duval bodies, which are glomerulus-like structures with a central blood vessel surrounded by tumor cells, are seen (yolk sac tumor) (*1B*). In another area of the specimen, immature neural tissue (*upper right*) and skeletal muscle with stromal tissue (*lower left*) are also seen (immature teratoma) (*1C*). (*1B, 1C*) hematoxylin-eosin stain,  $\times 100$ .

hepatitis C virus antibody were negative. Concurrently, the patient developed progressive pancytopenia; the hemoglobin was 11.2 g/dL, the white blood cell count was  $2.64 \times 10^9/L$  without abnormal cells, and the platelet count was  $33 \times 10^9/L$ . The serum ferritin level was increased to 1,800 ng/mL. The patient had no enlarged surface lymph nodes, and abdominal CT showed mild hepatosplenomegaly. Bone marrow aspiration showed normocellular bone marrow with 2.8% of activated macrophages engulfing the blood cells (Fig. 2). Therefore, the patient was diagnosed as having HPS about three months after tumor resection. After treatment with corticosteroid (prednisolone 30-60 mg/day) for 3 weeks, his liver dysfunction improved (total bilirubin, 1.67 mg/dL; AST, 35 IU/L; ALT, 51 IU/L). However, his intermittent high fever persisted, and the platelet count decreased to  $10 \times 10^9/L$ . The serum ferritin level also increased to 2,420 ng/mL. Because this patient's condition was refractory to corticosteroid treatment, the patient was referred to our hospital, and the cause of the HPS was investigated. There were no findings of active bacterial or viral infection, such as Epstein-Barr virus and cytomegalovirus. Disseminated intravascular coagulation syndrome, autoimmune disorders, and other ma-



**Fig. 2.** Histological examination of bone marrow samples. (*2A*) Multiple activated macrophages (*arrows*) are seen. (*2B*) Hemophagocytic cell engulfing blood cells. (*2A*) May-Giemsa stain,  $\times 100$ ; (*2B*) May-Giemsa stain,  $\times 1,000$ .

lignant diseases, such as malignant lymphoma, were not present. The expressions of familial hemophagocytic syndrome-related proteins (perforin, Munc13-4 and syntaxin11) in blood cells were normal. With respect to the germ cell tumor, the serum  $\alpha$ -fetoprotein (AFP) level decreased from 2,530 ng/mL to 44 ng/mL after surgery and then increased again to 103 ng/mL at the time of admission to our hospital. Positron emission tomography (PET)-CT revealed multiple bone metastases in the left humeral head and iliac bone. This early exacerbation of the germ cell tumor during the course of HPS strongly suggested a relationship between the HPS and the germ cell tumor. Corticosteroid therapy was then stopped, and chemotherapy with the BEP (bleomycin, etoposide, and cisplatin) regimen was started. Because the patient developed bleomycin-related lung complications, he then received one course of EP (etoposide and cisplatin) and three courses of the VIP (vinblastine, ifosfamide, and cisplatin) regimen. The patient's platelet count increased to  $86 \times 10^9/L$  after EP therapy, and it was  $203 \times 10^9/L$  after four courses of VIP therapy. Serum AFP and ferritin levels also decreased to 15.4 ng/mL and 383.3 ng/mL, respectively. However, PET-CT revealed residual tumor in the left humeral head. The patient then underwent autologous peripheral blood stem cell transplantation (PBSCT) with conditioning consisting of high dose ICE (ifosfamide, carboplatin, and etoposide). Unfortunately, two months after PBSCT, lung and bone metastases developed. The salvage TIP (paclitaxel, ifosfamide, and cisplatin) regimen was not effective, and the patient was transferred to another hospital for palliative care. His platelet count remained relatively low (around  $100 \times 10^9/L$ ) after PBSCT; however, bone marrow examination was not performed, and there were no other findings that strongly suggest HPS at the time of post-transplant recurrence of the germ cell tumor.

## DISCUSSION

When the immune system is activated, it is usually then down-regulated after the pathogen is eliminated by cytotoxic cells, such as macrophages, natural killer (NK) cells, and T cells. However, when the activation of the immune system is sustained due to a functional disorder of the cytotoxic cells or the existence of continuous stimulation, activated T cells, NK cells, and macrophages continue producing cytokines, such as interferon- $\gamma$ , interleukin-1, interleukin-6, and tumor necrosis factor- $\alpha$ . Dysregulated hypercytokinemia causes several conditions, such as pancytopenia, liver dysfunction, and coagulopathy. In familial hemophagocytic lymphohistiocytosis, abnormal expression of cytotoxic granule-associated proteins, such as perforin, Munc13-4, and syntaxin11, has been reported.<sup>4</sup> In the present case, the expression of these proteins was not decreased. Furthermore, no other disorders, such as infection or autoimmune disease, which are well

known to cause HPS, were found. During the course of HPS, the germ cell tumor progressed, suggesting a close relationship between the tumor and HPS. Although the present case of HPS was refractory to corticosteroid therapy, the patient had a good response to EP and the VIP regimen including etoposide, which is also known to be a key drug for severe HPS. Tumor reduction and the etoposide-based regimen might have contributed to the resolution of HPS.

An association between non-seminomatous germ cell tumors and hematological malignancies has been reported.<sup>5</sup> This rare but unique syndrome involves relatively young males, and the primary sites of germ cell tumors are exclusively in the mediastinum. Mediastinal germ cell tumors often precede the hematological malignancies by several months. These germ cell tumors frequently have yolk sac elements, and hematologic neoplasia may arise as a consequence of multipotential differentiation of malignant germ cells within the yolk sac. Acute megakaryoblastic leukemia and malignant histiocytosis are frequently observed hematologic abnormalities. Malignant histiocytosis includes true histiocytic sarcoma<sup>6,7</sup> and reactive histiocytosis with a hemophagocytic appearance.<sup>8,9</sup> In the present case, HPS was thought to have been caused by a reactive process, since massive proliferation of atypical histiocytes was not evident. Three cases of reactive HPS associated with germ cell tumors have been reported previously.<sup>8,9</sup> Unlike the present case, these 3 cases were refractory, with rapid deterioration and death despite several treatment approaches, including chemotherapy and/or radiation therapy. The difference in the response may be due to the tumor burden. In the present case, HPS developed postoperatively, and the tumor burden was smaller than in previous cases because of the tumor resection. The exact mechanism involved in cytokine overproduction in HPS associated with mediastinal germ cell tumor remains unknown. It has not been conclusively demonstrated which is the main cell that release the cytokines, the germ cell tumor, especially yolk sac elements, or the activated T cells in response to tumor antigens. In the present patient, recurrent fever developed one month after surgery. As one of the background factors, surgical stress might influence the cytokine network, though there were no surgical complications or infections in the perioperative period.

Primary mediastinal non-seminomatous germ cell tumor has a poor prognosis; the 5-year overall survival rate is nearly 50% with conventional doses of cisplatin and etoposide-based chemotherapy. Many clinical trials involving high-dose chemotherapy (HDCT) with autologous stem cell transplantation have been performed. Recent randomized trials in the USA and Europe involving patients with metastatic or poor-risk germ cell tumors demonstrated that routine use of HDCT as first-line treatment did not improve treatment outcome.<sup>10,11</sup> However, in the USA trial, a higher proportion of a subgroup of patients with unsatisfactory serum tumor

marker declines during the first two cycles of BEP had a more durable complete remission when treatment was changed to HDCT.<sup>10</sup> These results demonstrate the need to identify patients refractory to standard therapy early, and investigational chemotherapy approaches such as HDCT should be considered for these patients. In the present patient, residual tumors were found by PET-CT after four courses of VIP therapy; therefore, autologous peripheral stem cell transplantation was performed. Unfortunately, the present patient experienced early recurrence after first-line treatment with HDCT. Development of effective therapy, including the optimal timing and the best regimen for HDCT, is needed to improve the survival of poor-risk patients with mediastinal germ cell tumor.

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