Mediastinal Germinoma Associated with Hemophagocytic Lymphohistiocytosis: A Case Report

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ABSTRACT

Background: Malignancy-associated hemophagocytic syndrome (MAHS), a secondary form of hemophagocytic lymphohistiocytosis (HLH), can be found with several types of malignancy. It can be manifested either before or after the diagnosis of the underlying malignancy. However, mediastinal germinoma associated HLH has never been reported in previous literatures.

Case report: A 13-year-old boy presented with prolonged fever for 10 days with marked hepatosplenomegaly and progressive bicytopenia. Additional investigations demonstrated hyperferritinemia and increased hemophagocytic activity in the bone marrow without evidence of malignancy, compatible with the diagnosis of HLH. He responded well to the HLH-treatment with intravenous immunoglobulins and dexamethasone, but the HLH recrudesced 5 days later. Further investigation revealed anterior mediastinal mass. He quickly deteriorated afterwards and developed pulmonary hemorrhage leading to respiratory failure and died on the following day. Result of the post-mortem tumor biopsy was consistent with mediastinal germinoma.

Conclusion: MAHS should be considered in HLH patients who do not respond well or develop recurrence after the appropriate HLH-immunochemotherapy. HLH associated with mediastinal germinoma is rare and fatal. Making diagnosis of the underlying mediastinal germinoma is complicated and challenging. Early diagnosis and prompt treatment of HLH along with the appropriate treatment of germinoma might be the important key for the treatment success.

Keywords: Germ cell tumor, hemophagocytic lymphohistiocytosis, malignancy-associated hemophagocytic syndrome, mediastinal germinoma

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life threatening clinical event with high mortality rate. The common clinical manifestations include fever, splenomegaly, pancytopenia and proliferation of histiocytes with increased hemophagocytic activity in the bone marrow or extramedullary organs.[1]

HLH is classified into two categories, primary and secondary HLH. Malignancy-associated hemophagocytic syndrome (MAHS), a secondary HLH (sHLH) associated with malignancy, has been previously reported with various cancers including hematologic malignancies and, less frequent, solid tumor.[2-4] Mediastinal germinoma associated with HLH is very rare and, to

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our knowledge, has never been published. We reported herein a 13-year-old boy with mediastinal germinoma, presented with MAHS.

CASE REPORT

A previously healthy 13-year-old boy presented to the local hospital with fever for 3 days, anemia and mild hepatosplenomegaly. His initial complete blood count (CBC) revealed moderate anemia and thrombocytopenia (Table 1). Other investigations including thick film and thin film for malaria, dengue NS-1 antigen, dengue IgM and IgG antibody, and leptospirosis IgM antibody were negative. He was treated with intravenous ceftriaxone and blood transfusion. He remained febrile, but clinically well.

He was transferred to our hospital on day 10 of the fever. Physical examination revealed high grade fever (T 39.4°c) without identifiable source of infection, marked pallor and marked hepatosplenomegaly. His peripheral blood smear showed bicytopenia without blast cells or hemolytic blood picture. Results of the infectious study were negative for malaria, *mycobacterial tuberculosis, leptospira, Orientia tsutsugamushi, Rickettsia typhi* and Ebstein-Barr virus. Chest x-ray (CXR) and bone marrow aspiration (BMA) were unremarkable. He still received treatment with ceftriaxone and doxycycline.

On day 15 of the illness, he still had high grade fever, progressive bicytopenia and hyperferritinemia (Table 1). The subsequent BMA demonstrated increased histiocytes with hemophagocytic activity, without evidence of malignancy (Fig 1). He was diagnosed as sHLH and was treated with intravenous immunoglobulins and dexamethasone as per the HLH-2004 treatment protocol.[1] He responded well and became afebrile within 24 hours. Nevertheless, he still had hepatosplenomegaly and bicytopenia.

Six days later (day 22), he developed another episode of high grade fever with hypotension and respiratory distress. His hemoculture was positive for *Methicillin-sensitive Staphylococcus aureus.* He was treated with broad spectrum antibiotics (meropenem, amikacin, vancomycin), due to suspected septic shock. His CXR and chest computed tomography (CT) scan demonstrated anterior mediastinal mass (Fig 2). Serum tumor markers including alpha-fetoprotein (AFP) and β-subunit of human chorionic gonadotropin (β-HCG) were within normal range. The subsequent blood tests, including CBC, serum ferritin and fibrinogen, still showed evidence of HLH (Table 1). Therefore, he was arranged for tumor

TABLE 1. Result of the investigations on various days of the clinical course.

Tests	Day 3	Day 10	Day 15	Day 17	Day 19	Day 22
Hemoglobin (g/dl)	7.6	6.8	5.7	7.1	6.9	5.3
WBC (/mm^3)	5,300	3,160	2,600	6,880	7,510	4,310
ANC* (/mm^3)	3,604	2,101	1,440	5,390	5,850	2,887
Platelet count (/mm^3)	80,000	62,000	16,000	24,000	29,000	11,000
Reticulocyte count (%)	-	0.99	-	-	-	-
AST[?]/ALT (U/l)	-	34/27	36/49	37/39	42/38	319/276
TB[ll]/DB (mg/dl)	-	0.6/0.1	1.2/0.7	1.1/0.6	0.8/0.5	3.6/2.2
Ferritin (ng/ml)	-	767.6	1105	767.4	-	35,267
Triglyceride (mg/dl)	-	121	151	-	-	120
Fibrinogen (g/l)	-	2.87	1.64	2.55	2.03	1.47
LDH** (U/l)	-	508	-	-	559	13,758
AFP[??] (IU/ml)	-	-	-	-	-	3.1
β-HCG (mIU/ml)	-	-	-	-	-	4.91

*ANC = absolute neutrophil count, [?]AST = aspartate aminotransferase, ALT = alanine aminotransferase, [ll]TB = total bilirubin, DB = direct bilirubin, **LDH = lactate dehydrogenase, [??]AFP = alpha-fetoprotein, β-HCG = β-subunit of human chorionic gonadotropin

biopsy with a plan of adding etoposide as an additional treatment for HLH. Unfortunately, he deteriorated quickly afterwards. He developed pulmonary hemorrhage leading to respiratory failure, and died of HLH on the following day. Result of the post-mortem mediastinal mass autopsy was consistent with germinoma. Splenic autopsy revealed histiocytosis and moderate increase of hemophagocytic activity, compatible with hemophagocytic syndrome.

DISCUSSION

MAHS is rare and evidently fatal. It usually occurs at the initial presentation of the underlying malignancy and sometimes even masking the clinical presentation of the malignancy itself,[3-5] similar to our patient. However, it can also happen anytime during the cancer treatment.[3,6]

Mediastinal mixed germ cell tumor (GCT) is responsible for most MAHS caused by solid tumor.[5,7-9] In contrast, mediastinal germinoma, a more common, but less malignant subtype of GCT, has never been reported as the cause of MAHS. It is believed that the dysfunctional immune system caused by cytokine production from malignant cell or chemotherapy treatment accounts for the development of MAHS.[2] In patient with mediastinal GCT, thymus involvement by the tumor cell might result in the T-cell-dysregulation leading to a development of MAHS.[5] Simultaneous infection may be an additional trigger for MAHS in some patients,[3] as seen in our patient at the time of HLH recrudescence.

In the present patient, he was diagnosed with sHLH, which was likely associated with infection, and responded well to the initial HLH-treatment. However, there was no identifiable source of infection and the recrudescence of HLH few days later indicated that the cause of sHLH might not originate from an infection. Further investigation demonstrated anterior mediastinal mass, but the tumor markers were negative. Therefore, pathological result is required to confirm diagnosis in such a situation, contrary to patients with mixed GCT which can be diagnosed easily

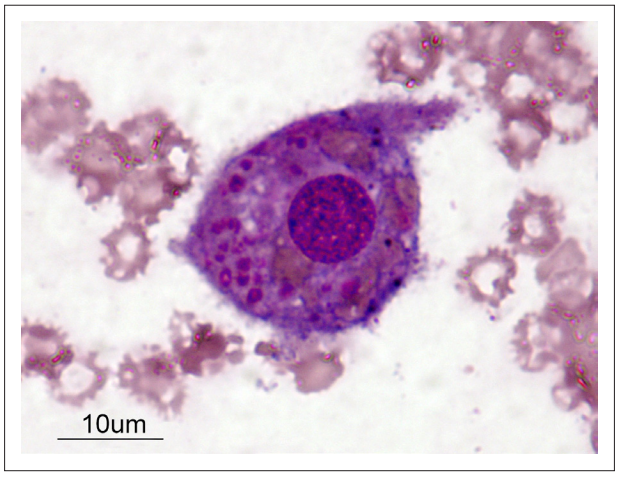
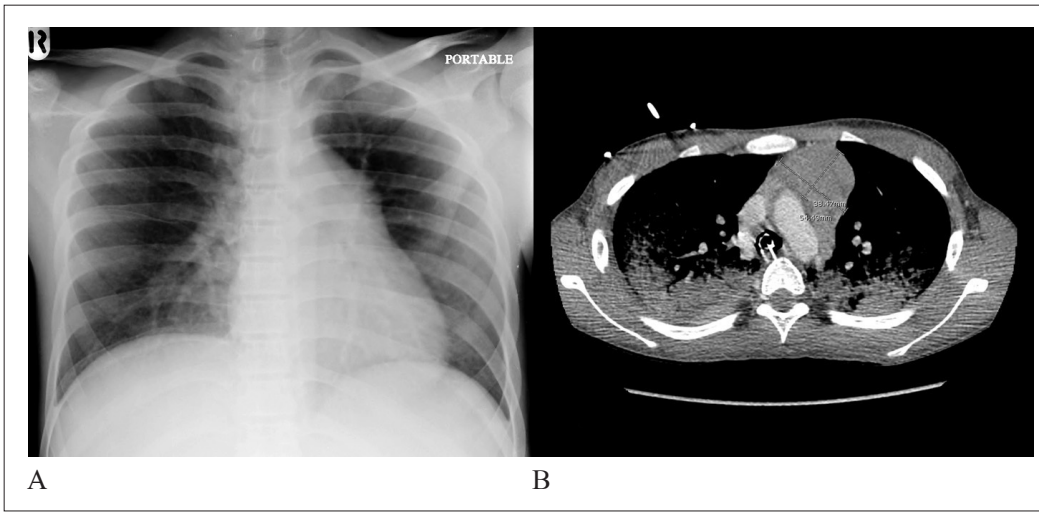


Fig 1. Reactive histiocyte with increase hemophagocytic activity in the bone marrow.
(Wright stain).



A B

Fig 2. Anterior mediastinal mass: (a) with superimposed interlobar thickening (Chest x-ray); (b) with pulmonary hemorrhage and pleural effusion (CT scan).

based on the positive tumor markers result. This issue lead to the diagnostic difficulty and diagnostic delay in our patient.

Most experts believe that controlling inflammation process before starting disease-specific chemotherapy is an appropriate option for treating MAHS.[2] However, the efficacies of this treatment approach in MAHS with mediastinal GCT are still not known. Most patients in the previous reports responded poorly to the treatment with HLH-based immunochemotherapy, disease-specific chemotherapy and/or allogeneic bone marrow transplantation.[5,7-9] The only one survivor, to knowledge, was treated by the combination of HLH-treatment simultaneously with the standard chemotherapy for GCT.[10] However, another patient who received the same treatment approach did not survive.[8] To date, there is no standard treatment of mediastinal GCT associated with HLH. Our patient received only HLH-based immunochemotherapy, but he died before he got the diagnosis and treatment of mediastinal germinoma. Difficulties in diagnosis of underlying tumor causing the delay of specific treatment might have rendered the dismal outcome in our patient.

CONCLUSION

Mediastinal germinoma associated with MAHS is very rare and difficult to diagnose and treat. MAHS should be considered in sHLH patients who have no identifiable source of infection and do not respond well or develop recurrence despite receiving appropriate HLH-treatment, so proper investigation e.g. serum LDH and tumor markers including AFP and β-HCG is recommended. In addition to that, a CXR including lateral view and/or chest/abdomen CT to seek for an underlying malignancy should be considered in those who do not have evidence of leukemia/lymphoma, especially in older children. Early diagnosis of the underlying malignancy and prompt treatment of HLH to control the inflammatory process along with the specific treatment of germinoma might play the important role for the treatment success.

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