Hemophagocyte Lymphohistiocytosis Secondary to Bilateral Epididymal Diffuse Large B-Cell Lymphoma

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Abstract We report a rare case of hemophagocytic lymphohistiocytosis (HLH) secondary to bilateral epididymal lymphoma. The patient is a man of 46 years old. He suffered fever 5 months before the admission. Physical examination shows splenohepatomegalia without lymphadenopathy. Laboratory studies revealed pancytopenia and coagulopathy, hyper ferritin level, large foamy macrophages containing other hematopoietic elements in bone marrow. After treatment with HLH-04 protocol, the patient recovered, but relapsed 1 month later and suffered pudendal pain. A color Doppler of the scrotum shows bilateral epididymis swollen. Pathological diagnosis of biopsy is diffuse large B cell lymphoma (DLBCL). After two cycles cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab together with intrathecal injections, the tumors on the epididymides disappeared, but relapsed intracalvarium. The patient stopped treatment due to financial reasons. Hemophagocytic lymphohistiocytosis secondary lymphoma in a sanctuary site has not been reported before and should not be ignored. Transplantation is necessary for long-time survival.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a lethal syndrome that is mediated by the immune system. Based on the pathogenesis of HLH, the syndrome can be classified as inherited or acquired. The former usually arises in infants and has been attributed to defects in the perforin

function of the cytolytic granules of NK cells and cytotoxic T lymphocytes [1]. The acquired forms of HLH have been associated with infections, inflammatory diseases and malignancies. Lymphoma is the primary malignancy-related cause of HLH [2, 3]; however, HLH secondary to lymphoma in a sanctuary site, such as the central nervous system, testis or epididymides, has not been reported. The present study reports a rare case of HLH secondary to bilateral epididymal lymphoma.

Case Report

A 46-year-old man was admitted on April 27, 2011 for persistent fever. Five months before his admission, he suffered from periodic fever, vibration white fingers, discontinuous arthralgia in his arms and legs, jaundice, abdominal distention, anorexia and loss of body weight. He was admitted to the local hospital and diagnosed with “pneumonia”. After 10 days of treatment with ofloxacin, the patient’s condition worsened, and he was transferred to our hospital for further treatment.

His physical exam was notable because he had a temperature of 39.3 °C, his blood pressure was 110/60 mm Hg, his respiratory rate was 28 breaths per minute and his pulse was 100 beats per minute. The patient had pallor, mild jaundice, splenohepatomegalia, 3 + bilateral lower extremity edema, and scrotal edema. Interestingly, the patient did not have lymphadenopathy of the scrotum, and we did not find any joint swelling.

Laboratory studies revealed pancytopenia and coagulopathy (Table 1), but an antinuclear antibody (ANA) screen was negative. A bone marrow aspirate revealed hypercellular bone marrow that contained maturing trilineage hematopoiesis with prominent megakaryopoiesis and

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hyperplastic dyserythropoiesis. We also noticed occasional large foamy macrophages containing other hematopoietic elements (Fig. 1). A color Doppler of superficial lymph nodes and retroperitoneal lymph nodes confirmed that there was no lymphadenopathy of the scrotum. The chest and abdominal computerized tomography showed an enlargement of the liver and spleen, but no lymphadenectasis was seen in the mediastinum and retroperitoneum.

The patient was diagnosed with HLH. Due to the previous vibration white fingers and discontinuous arthralgia, HLH was assumed to be secondary to a rheumatic disease. The bilateral edema of the lower extremities and the scrotum was attributed to hypoproteinemia. On May 3, etoposide, cyclosporin A and dexamethasone were administered according to the protocol suggested by HLH-2004 [4]. The fever was alleviated on the second day of treatment, and the patient showed significant improvements. Although bilateral lower extremity edema improved after correcting the hypoproteinemia, the sanctuary edema did not change.

On June 1, the patient suffered a fever and experienced pudendal pain. Epididymitis was suspected, and antibiotics were introduced; however, the pudendal pain did not improve. An auxiliary examination (Table 1) suggested a relapse of HLH. A color Doppler of the scrotum found a normal size and signal of the testis. Fluid areas were explored, and the maximum distance between the front and rear of the scrotum was 1.0 cm on the left and 1.9 cm on the right. The depths of the epididymides were 1.4 cm on the left and 2.2 cm on the right. The caput, body and cauda of the epididymides were swollen and visibly distended, and scattered solid hypoechoic areas of unequal sizes were distributed throughout the epididymides, which appeared to be “grape-like”. In addition, the hypoechoic areas involved the spermatic cord and partly invaded the testis. The blood flow signal was abundant in both of the epididymides.

A right scrotal investigation was performed by biopsy. Routinely processed histological sections revealed malignant lymphoma. Immunohistochemical staining identified the lymphatic cells as B cells by the expression of CD20 antigen (Fig. 1). We also investigated the lymphoma stage using computerized tomography of the abdomen and thorax. The patient was finally diagnosed with HLH secondary to diffuse large B cell lymphoma (DLBCL) of the epididymides, which was staged as I(B). He received cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (R-CHOP) four cycles. In addition, the patient received intrathecal injections during each cycle of chemotherapy. After two cycles of R-CHOP, the tumors on the epididymides disappeared; however, the patient suffered from headaches on November 14. Multifocal scattered lesions of increased signal intensity were observed on a brain MRI, which suggested lymphoma infiltration. Unfortunately, the patient stopped treatment due to financial reasons.

Discussion

Malignant lymphoma of the scrotal contents is usually confined to the testis, and primary lymphoma of the epididymis is rare. Indeed, a review by Vega [5] revealed that primary lymphoma of the epididymis had been reported in six patients prior to 2001. In addition, only four additional cases have been reported in the literature since 2001 [5–8]. The mean age of the 10 patients with reported primary lymphoma of the epididymis was 42.6 years (the range was 20–73 years). Eight cases were diagnosed as non-Hodgkin's lymphoma: three cases of diffuse large cell (DLC) lymphoma, two cases of intravascular large cell lymphoma (IVL), two cases of follicular large cell lymphoma (FL), and one case of low-grade B cell lymphoma of mucosa-

Table 1 Laboratory examinations of the patient at different periods

	At diagnosis (2011-5-2)	After treatment (2011-5-31)	At relapse (2011-6-7)	Range
Neutrophils ($\times 10^9/L$)	0.7	5.0	5.5	2.0–7.5
Hemoglobin (g/dL)	4.8	9.3	8.7	12–16
Platelets ($\times 10^9/L$)	33	100	80	100–400
APTT (s)	51.8	36.5	39.3	24–38
PT (s)	14.0	12.8	14.8	10.8–6.5
Fibrinogen (g/L)	2	4.07	3.76	2–4
Ferritin (ng/ml)	11,782	1,388	2,440	16–323
Triglyceride (mmol/L)	4.1	2.74	3.7	0.22–1.7
Alanine transaminase (IU/L)	100	23	73	5–40
Aspartate transaminase (IU/L)	221	29	98	5–48
Bilirubin ($\mu\text{mol/L}$)	32.5	20	70.6	3.4–20.5
Albumin (g/L)	24	37	29	35–55

Fig. 1 The Pathological Changes. **a** Bone marrow smears showed prominent hemophagocytosis. **b** HE stain showing a diffuse, pleomorphic large tumor cells infiltrate, the pleomorphic large tumor cell with vesicular nuclei and prominent nucleoli. 400X.

c Immunohistochemical stain for CD20 showing membrane positive of the tumor cells. **d** Immunohistochemical stain for MUM1 showing nuclear staining of the tumor cell

associated lymphoid tissue (MALT). In seven of the ten cases, the neoplasm involved the right epididymis, whereas two cases involved the left epididymis. Only one case involved both epididymides [9]. The present case is the second case of primary lymphoma involving both epididymides.

Although HLH is extremely rare in Western areas of the world, it is common in Asia. In Japan, the annual incidence of HLH was estimated as 1 in 800,000 per year (primarily the acquired form) [3]. HLH was the most common in NK/T cell lymphoma (i.e., up to 24.7 %) [10]. The mechanism of triggering HLH in lymphoma has not been fully elucidated, but a mutation of the perforin gene is partly responsible [11, 12]. However, HLH secondary to lymphoma of a sanctuary site, such as the central nervous system, testis or epididymides, has not been reported.

Data on the prognosis and treatment optimization of primary epididymis lymphoma are limited. Vega [5] reviewed the prognosis of eight patients. Five patients reached complete remission and survived without relapse, but the follow-up was too short (less than 1 year in 5 of them) to draw conclusions. In a long-term follow-up of 373 patients with primary testicular DLBCL, the outcome appeared to be poor. B cell lymphoma is characterized by a particularly high risk of extranodal relapse, even in cases with localized disease at diagnosis [13]. The combination of chemotherapy and R-CHOP, central nervous system prophylaxis and contralateral testis irradiation has greatly

improved the prognosis of patients with testicular lymphoma [14].

The prognosis of HLH secondary to lymphoma is unfavorable, and the median survival time is less than 40 days [2, 10]. Importantly, survival has been shown to be dependent on the type of lymphoma. Indeed, B cell lymphoma has been reported to be much more favorable than T–NK cell lymphoma [3]. Machaczka [15] examined eight patients and found that only one patient with HLH-04 who was treated with an allogeneic stem cell transplant survived. In another article by Tong [2], long-term survival was achieved in four out of 29 patients, three of which received autologous stem cell transplants. The present HLH patient relapsed during the fourth week of treatment after decreasing the etoposide and immunosuppressive regimen, which suggested that regimen like HLH-04 alone is not sufficient to control lymphoma. We believe that autologous or allogeneic stem cell transplantation is preferable for long-term survival in patients with HLH secondary to lymphoma.

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