Primary Bilateral Adrenal NK/T Lymphoma Revealed by Hemophagocytic Syndrome - A Case Report and Literature Review

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Abstract

Primary adrenal lymphoma is a malignant tumor that originates in lymph nodes and extranodal lymphoid tissues, but the adrenal gland has no lymphoid tissue, so the pathogenesis is not clear. NK/T-cell lymphoma is a rapidly progressing hematological malignancy. Reports of primary adrenal NK/T-cell lymphoma are rare. On September 11, 2018, we first discovered a case of primary adrenal NK/T lymphoma with hemophagocytic syndrome as the first manifestation.

Keywords: Primary adrenal lymphoma; NK/T-cell lymphoma; Hemophagocytic syndrome

Introduction

Primary Adrenal Lymphoma (PAL) is very rare extranodal lymphoma, accounting for less than 1% of all non-Hodgkin’s lymphoma (NHL) and 3% of extranodal lymphoma [1,2]. According to the 2008 WHO definition, the two most common subtypes of PAL are Diffuse Large B-Cell Lymphoma (DLBCL) (78%) and peripheral T-cell lymphoma (7%). Natural killer (NK)/T-cell NHL (NK/T NHL) is a highly invasive hematological malignancy that occur most commonly (80%) in the nose and upper aerodigestive tract, less commonly (20%) in sputum, nasopharyngeal and oropharynx. Currently only 2 cases of primary adrenal NK/T cell lymphoma have been reported [3,4]. We report a case of a 69-year-old man who had a NK/T NHL associated with Hemophagocytic Syndrome (HHS).

Case Presentation

A 69-year-old previously healthy man was admitted with a chief complaint of intermittent fever for one month and skin ecchymosis for 3 days on September 11, 2018. Body temperature fluctuated between 38.5°C and 40°C without chills and joint muscle pain. Physical examination after admission indicated palpable splenomegaly (2 cm). Laboratory tests indicated as follows: WBC 2.42 × 10^9/L, NE 1.3 × 10^9/L, Hb 125 g/L, PLT 22 × 10^9/L; ALT 63 U/L, AST 80 U/L, ALB 28.3 g/L, LDH 522 U/L, K+ 3.20 mmol/L, BUN 4.9 mmol/L, SCR 154 mmol/L, UA 154 mg/dL, CRP 22.7 mg/L, PCT 0.23 ng/ml; β2-MG: 5.59 mg/L, TG 5.73 mmol/L; PT 14.4s, APTT 40.5s, FIB 0.48 g/L, D-Dimer 2.80 mg/L, ferritin 6,520 ng/ml; EBV capsid antigen IgG positive, EBV nuclear antigen IgG positive, EBV DNA<1 × 10^2 copies/ml, CD25 7,126 pg/ml. Chest CT showed increased lung texture and no pleural effusion. Abdominal ultrasound showed normal spleen size 110 mm × 55 mm, with no space-occupying lesions. Bone marrow aspiration and biopsy showed phagocytosis, as shown in Figure 1.

Adrenal plane scan + enhanced CT: CT plain scan shows bilateral adrenal enlargement, right side: 60 mm × 40 mm × 27 mm; left side: 60 mm × 49 mm × 21 mm and bilateral adrenal arteriovenous phase of enhanced scan shows slight gradual uneven enhancement (Figure 2A-2C). PET-CT showed high FDG uptake in both adrenal glands, SUVmax 17.4 on the right and SUVmax 15.6 on the left (Figure 2D). CT-guided puncture of the right adrenal gland: Adrenal tissue T-cell lymphoma, immunohistochemistry: CD2 (+), CD3 (+), CD20 (-), CD30 (-), CD56 (+), CD7 (+), LCA (+), Ki67 (positive >75%), CK (-), EMA (-), TIA-1 (+), EBER (+) (Figure 3).

Final diagnosis: 1. Primary bilateral adrenal NK/T cell lymphoma stage I-EB 2. Hemophagocytic syndrome.

Dexamethasone (Dex) 10 mg/m^2/d was given on September 18, 2018. After 10 days, Dex was reduced to 5 mg/m^2/d; etoposide was given at a dose of 75 mg/m^2 biw. Cryoprecipitation, platelet
and fibrinogen were given to improve coagulation disorder. After 5 days, the patient's body temperature gradually returned to normal. Coagulation function test on day 8 showed: PT 11.7s, APTT 38.2s, FIB 1.56 g/L, D-Dimer 1.27 mg/L. P-GeMOX scheme given on day 15 as follows: Gemcitabine 1000 mg/m² iv d1, d8; Oxaliplatin 100 mg/m²; d1, Pegaspargase 2000 U/m² im. On the 23rd day, platelets increased (27 × 10⁹/L), complete blood count on the 30th day: WBC 6.4 × 10⁹/L, Hb 105 g/L, PLT 138 × 10⁹/L. After 14 days interval, second cycle of P-GEMOX regimen was given. After that, GDP regimen was implemented in 21-day cycle for cycles: Gemcitabine (1000 mg/m² intravenously over 30 min on days 1 and 8), dexamethasone (20 mg/day orally on days 1-4 and days 11-14), and cisplatin (25 mg/m² intravenously over 60 min on days 1-3). Evaluation with contrast enhanced CT: The bilateral adrenal glands shrank to normal size with peritoneal effusion, as shown in Figure 4. The patient refused to receive radiotherapy. For now, this patient is stable for 9 months.

**Discussion**

Lymphoma is a malignant tumor originating from lymph nodes and extranodal lymphoid tissues, but the adrenal gland has no lymphoid tissue, so the pathogenesis of primary adrenal lymphoma is not clear. So far there is no clear definition of PAL, and most scholars have adopted the following standards: 1) confirmed unilateral or bilateral adrenal lymphoma; 2) no other organ tissue involvement after diagnosis for at least 6 months; 3) no evidence of leukemia [4]. Pathological diagnosis of adrenal NK/T cell lymphoma was made in this patient. PET-CT showed no invasion of other organs and bone marrow involvement, which was consistent with the diagnosis of primary adrenal NK/T cell lymphoma. Primary adrenal lymphoma often causes fever, backache, bloating, fatigue, weight loss, or adrenal insufficiency and pheochromocytoma as the first manifestations [5,6]. The multi-slice spiral CT and PET-CT examination are most helpful to make a diagnosis. Multislice spiral CT characteristics are marked enlargement of adrenal glands, but adrenal masses are more uniform in density and clear in boundary, usually without hemorrhage, cystic degeneration, necrosis and calcification. PET-CT characteristics are often involved the bilateral adrenal glands, adrenal gland volume, with high FDG uptake, no other lymphoma lesions. In addition, PET-CT plays an important role in differentiating primary from secondary, benign from malignant and in evaluating the curative effect after treatment. When clinical encounters fever, backache and suspected cases with unknown origin, attention should be paid to exclude invasion of deep organs. If PET-CT is confirmed adrenal mass, CT-guided puncture is the most direct method for definite diagnosis.

Hemophilic Syndrome (HPS), also known as Hemophilic Lymphohistiocytosis (HLH), is a kind of excessive inflammatory response syndrome caused by primary or secondary immune abnormalities. This abnormal immune regulation is mainly caused by abnormal activation and proliferation of lymphocyte, monocyte and macrophage system, secretion of a large number of inflammatory cytokines and a series of inflammatory reactions. Primary HPS is caused by hereditary immune disorders, and secondary HPS is caused by tumors, infectious diseases or autoimmune diseases. Lymphoma is the leading cause of HLH in adults [7], especially in NK/T-cell

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**Figure 1:** There is prominent phagocytosis of erythroid precursors in this view.

**Figure 2:** A) shows bilateral adrenal CT; B) shows that the adrenal gland enhances the CT arterial phase; C) shows that the adrenal gland enhances the CT venous phase; D) shows PET-CT shows high uptake of the bilateral adrenal FDG.

**Figure 3:** A) Shows needle puncture of the adrenal gland; B) CD3⁺; C) CD7⁺; D) CD2⁺; E) EBER⁺; F) CD56⁺; G) HE⁺; H) Ki-67⁺.

**Figure 4:** A) Shows the enhanced CT image of adrenal gland in venous phase, B) Shows the enhanced CT image of adrenal gland in arterial phase.
lymphoma. HLH can occur before the diagnosis of lymphoma, or at the same time as diagnosis or when lymphoma progresses or relapses. The patient has fever for one month, splenomegaly, leukopenia and thrombocytopenia, fibrinogen decreased, ferritin increased significantly, sCD25 level increased, and Hemophagocytic cells were found in bone marrow, according to HLH-2004 diagnostic criteria [8], the HLH diagnosis was established.

The mechanism of Extranodal NK/T cell Lymphoma (ENKTL) complicated with HLH is not clear. Wen et al. [9] found that the mutation of E3SIT gene V410A in NK/T cell lymphoma resulted in the release of inflammatory factors after the activation of NK-kβ signaling pathway in tumor cells. TNF and IFN-gamma could further promote the activation of peritumoral macrophages and secrete a large number of cytokines to form a cytokine storm. Jia et al. [10] analyzed 202 patients with extranodal NK/T-cell lymphoma and revealed that the cumulative incidence of NK/T-LAHS was 11.4%. Among them, younger age, bone marrow involvement and lower serum albumin were independent risk factors for HLH in patients with extranodal NK/T-cell lymphoma. The 2-year survival rate of patients with extranodal NK/T-cell lymphoma was only 30.4% when HLH was concurrent.

Because HLH is a highly lethal disease with rapid progress, once suspected, relevant examinations should be carried out as soon as possible. When HLH is diagnosed, treatment should be given immediately. For cases with HLH before diagnosis of lymphoma, HLH-94 or DEP regimen is recommended before specific treatment of lymphoma [11,12]. This patient received a rapid inhibition of hemophagocytosis after receiving the HLH-94 regimen, which reduced the risk of early death and provided a chance for subsequent treatment.

At present, there is no unified treatment recommendation for primary adrenal lymphoma. Generally, surgery, combined chemotherapy, radiotherapy, autologous stem cell transplantation and prophylactic intrathecal injection of central nervous system are the main treatment regimens. Jinlong [13] and others believe that for those with large masses and no invasion of adjacent tissues and organs, early tumor reduction surgery and post-operative combined chemotherapy may get good results. Gao et al. [14] treated 56 ENKTL patients with P-gemox regimen. The ORR rate was 89.3%, CR rate was 72.5%, RR rate was 94.6%, CR rate was 89.3%, and OS rate and PFS rate were 90.7% + 4.0% and 89.14% + 4.2% respectively after four courses of P-gemox regimen and the GDP program achieved complete remission. After the HLH-94 program was given to this patient, the p-gemox program and the GDP program achieved satisfactory results. Due to fewer reported cases, more therapeutic methods need to be accumulated for comparison. With the application of new drugs and cellular immunotherapy, the efficacy of primary adrenal NK/T-cell lymphoma needs to be further improved.

**Conclusion**

We report a case of bilateral adrenal NK/T-cell lymphoma with hemophagocytic syndrome as the first manifestation. When fever, low back pain and HLH of unknown cause appear in clinic, the possibility of primary adrenal NK/T-cell lymphoma should be considered, and further imaging and pathological examination should be carried out to confirm the diagnosis. After the HLH-94 program was given to this patient, the p-gemox program and the GDP program achieved satisfactory results. Due to fewer reported cases, more therapeutic methods need to be accumulated for comparison. With the application of new drugs and cellular immunotherapy, the efficacy of primary adrenal NK/T-cell lymphoma needs to be further improved.

**References**

