Case Report

Primary Testicular NK/T-Cell Lymphoma: A Study of Two Cases and Review of Literature

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ABSTRACT

Primary testicular NK/T-cell lymphoma is an extremely rare entity progressed rapidly. The aim of this study was to examine clinical and pathological features of primary testicular NK/T-cell lymphoma and to investigate the effective diagnosis and prognosis. In this paper, the two cases of primary testicular NK/T-cell lymphoma were observed by light microscopy, immunohistochemistry and examined by *in situ* hybridization for Epstein-Barr Virus (EBV) DNA and the literatures were reviewed. The two patients respectively present with bilateral and right-side painless testicular enlargement. The morphology of neoplastic cells of case 1 were small to medium, tumor cells of case 2 were small, medium and large mixed. The tumor cells grew diffusely with irregular and distort nuclear, destructed the organizational structure of the normal testis, and damaged blood vessels, meanwhile, coagulation necrosis was exist. Immunohistochemical staining of neoplastic cells showed positive for CD45, CD2, CD56, CD3ε (cytoplasm staining pattern), CD45RO and Granzyme B, and negative for CD57, CD20, CD79α, CD30, CK, MPO, TdT, *Bcl*-2 and PLAP were negative. In addition, the EBV DNA was detected in the lymphoma by In situ hybridization. In conclusion, the expression of CD56, CD3ε, and Granzyme B associated proteins and EBV examination by in situ hybridization play a vital role in diagnosis and differential diagnosis of primary testicular NK/T-cell lymphoma.

Key words: NK/T-cell lymphoma; Testis; CD56; EBV

INTRODUCTION

Primary testicular lymphoma comprises approximately 1%–2% of non-Hodgkin lymphoma (NHL) and 1%–7% of all testicular neoplasm. The majority are diffuse large B-cell lymphoma (DLBCL)[1]. Nasal type NK/T-cell lymphomas is an extremely rare entity and only twelve cases have been previously reported[2–4]. Two cases of primary testicular NK/T-cell lymphoma were reported in the study. Their morphological features were reviewed and immunophenotype was performed to explore clinicopathologic features, diagnosis and prognosis. Primary testicular lymphoma was defined as presenting with a clinically dominant testicular mass according to the diagnostic standard that adopted by the International Extranodal Lymphoma Study Group (IELSG)[1]. Nasal type NK/T-cell lymphoma was adopted by *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues* in 2008[5]. Two cases of primary testicular NK/T-cell lymphoma were collected at the First Affiliated Hospital of Chongqing Medical University in China from 1983–2006.

CASE REPORT

Case 1 was a 58-year-old man presented with painless bilateral testicular enlargement for two

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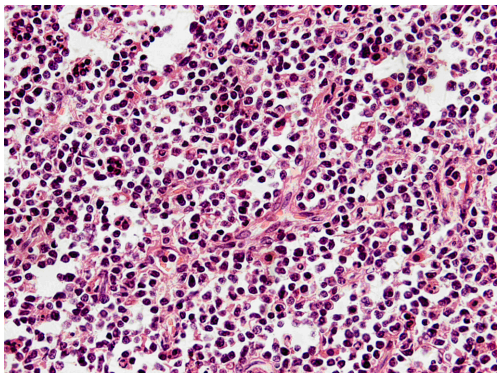

Figure 1. Primary testicular NK/T-cell lymphoma: histological features, (HE × 400).

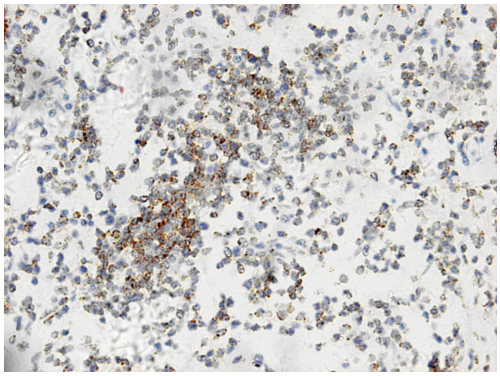

Figure 2. Primary testicular NK/T-cell lymphoma: tumor cells show staining for CD3ε antigen, (S-P × 400).

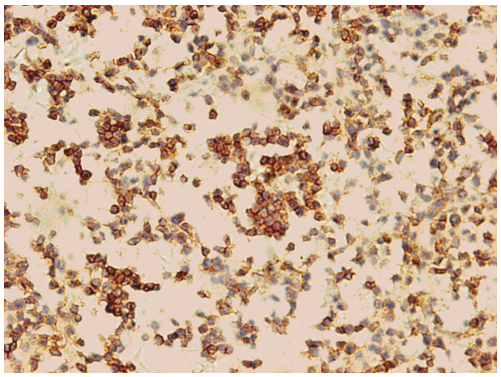

Figure 3. Primary testicular NK/T-cell lymphoma: tumor cells show staining for CD56 antigen, (S-P × 400).

months. Neither enlarged lymph nodes nor hepatomegaly and Splenomegaly were found by physical examination. Enlarged lymph nodes were not found in chest, abdominal and pelvic by mode-B ultrasonic scan. Peripheral blood and bone marrow laboratory testing showed no abnormalities. Ann Arbor staging was I_{EA}, International Prognostic Index (IPI) score was 0. The patient underwent bilateral radical orchiectomy and was diagnosed as "primary testicular extranodal NK/T-cell lymphoma, nasal-type".

The basic structure of testes had been destroyed, a large number of lymphoid cells diffusely infiltrated and grew between remaining seminiferous tubules with lymphoepithelial lesion. The areas of coagulation necrosis were limited (1 HPF) with a large number of nuclear debris and inflammatory cells infiltration. Some red blood cells and cell debris were phagocytized by histiocytes. The neoplastic cells of case 1 were small to medium-sized, which were round or oval-shaped with little cytoplasm and irregularly folded nuclei. Nuclear membrane was thin and nucleoli was not clear, mitosis were numerous (10–40/10 HPF) (Figure 1).

Immunohistochemistry showed reactivity for CD45, CD2, CD3ε (Figure 2), CD56 (Figure 3), CD45RO, Granzyme B and P53. Staining for CD57, CD20, CD79α, CD30, CK, MPO, TdT, BCL-2 and PLAP were negative.

Case 2 was 41 years old. The patient presented with a painless testicular mass on the right side which was 4 cm×3 cm×3 cm without fever, urgency and dysuria. The patient had been diagnosed as "chronic testicular inflammation" at a local hospital. Anti-inflammatory treatment was invalid. Three months late, the right testis mass increased to 10 cm×8 cm ×6 cm with smooth surface and rigid quality. Blood routine all decreased. Serum LDH increased and AFP and CEA were normal. Admission diagnosis was "right testicular tumor". The patient underwent right radical orchiectomy. Pathological diagnosis was "primary testicular extranodal NK/T-cell lymphoma, nasal-type". IPI score was 1 with I_{EA} stage.

Histological features of case 2 were almost the same with case 1. The neoplastic cells of case 2 were small, medium and large mixture with diffuse growth pattern. The cytoplasm was moderate in amount and often pale to clear, the nuclei of neoplastic cells were distortion with fine chromatin, mitosis 30–70/10 HPF. A small amount of plasma cells could be seen in background.

Immunohistochemistry staining of case 2 was same with case 1.

EBV genome was showed nuclear positive in the more than 50% neoplastic cells in all two cases in our study by In situ hybridization. Negative control compared with negative results.

Table 1. *Clinic and pathologic features of 14 cases of primary testicular NK / T-cell lymphoma*

Patient No.	Literatures	Age	Initial presentation	Immunophenotype						TCR gene rearrangement	Therapy	Metastatic sites	The cause of death	Survival time
				CD2	sCD3	CD45RO	CD3ε	CD56	EBER					
1	Sun et al.[6] 1993	32	Swelling of the right testis	-	N/A	-	-	+	+	-	Surgical resection + chemotherapy + radiotherapy	Spleen, bone Marrow	Gastrointestinal Bleeding	6
2	Chan et al.[7] 1996	47	Swelling of the left testis; loss of weight	+	-	+	+	+	+	-	Surgical resection + chemotherapy + radiotherapy	Nose, gastrointestinal tract	Gastrointestinal Bleeding	4
3	Chan et al.[7] 1996	71	Swelling of the left testis	+	-	+	+	+	+	-	Surgical resection	gastrointestinal tract	Gastrointestinal bleeding	2
4	Chan et al.[7] 1996	55	The left testicular swelling, weight loss, low fever	+	-	+	+	+	+	-	Surgical resection + chemotherapy	Skin, nasopharynx	Peritonitis, DIC	5
5	Güler et al.[8] 1999	35	Swelling of the right testis	N/A	N/A	N/A	N/A	+	+	N/A	chemotherapy + radiotherapy	Skin, contralateral testis, spleen	N/A	14
6	Bartolomé et al.[9] 2000	49	Swelling of the left testis	+	-	N/A	+	+	+	N/A	Surgical resection + chemotherapy	Peritoneum	Intracerebral hemorrhage	3
7	Bartolomé et al.[9] 2000	70	Swelling of the left testis	+	-	N/A	+	+	+	N/A	Surgical resection + chemotherapy	Retroperitoneal lymph nodes, skin	infection	5
8	Pérez-Vallés et al.[10]* 2000	47	Swelling of the left testis	-	N/A	-	-	-	+	N/A	Surgical resection + chemotherapy	Skin	Fever, Pancytopenia	12
9	Totonchi et al.[11] 2002	66	Swelling of the right testis	N/A	N/A	-	+	+	+	-	Surgical resection + radiotherapy	N/A	N/A	N/A
10	Kim et al.[4] 2003	52	Swelling of the right testis	+	N/A	+	+	+	+	N/A	Surgical resection + radiotherapy	Skin, CNS	leptomeningeal planting	8
11	Ballereau et al.[3] 2005	30	Swelling of bilateral testis, fever	N/A	-	N/A	+	+	+	-	Surgical resection + chemotherapy	CNS	meningitis, multiple organ failure	2
12	Zeng et al.[2] 2007	29	Swelling of the left testis	N/A	N/A	+	+	+	N/A	-	Surgical resection + chemotherapy	Spleen, liver, contralateral testis	pancytopenia, peritonitis, DIC	2
13	Present report	58	Swelling of bilateral testis	+	N/A	+	+	+	+	N/A	Surgical resection	N/A	N/A	N/A
14	Present report	41	Swelling of the right testis	+	N/A	+	+	+	+	N/A	Surgical resection	Systemic spread	Multiple organ failure	4

N/A = not available; DIC = disseminated intravascular coagulation; CNS=central nervous system; *the neoplastic cells of this case TIA-1$^+$, CD56$^-$, CD3$^+$ and CD45RO$^+$.

Both of these two patients underwent radical orchiectomy. Case 1 was lost to follow-up, case 2 experienced disseminated metastasis and died of multiple organ failure 4 months after diagnosis.

The clinicopathologic features and outcome of two cases of presenting report and twelve cases reported previously are summarized in Table 1.

DISCUSSION

Extranodal nasal-type NK/T-cell lymphoma is a quite rare non-Hodgkin lymphoma. It is more prevalent in Asia, Mexico, Central America and South America adults and is more common in men than in women. Clinical course was aggressive. The extranodal sites often to be affected are nasal cavity and nasopharynx, paranasal sinuses and hard palate. In addition, it also occurred as lymphomas in central nervous system (CNS), skin, lung, gastrointestinal tract and testes. It was recognized by WHO classification in 2008.

Primary testicular nasal-type NK/T-cell lymphoma is extremely rare. There are only 12 cases reported[2–4, 6–11] since Sun et al. first described one case in 1993. The primary testicular nasal-type NK/T-cell lymphoma whether treated or not, have the following unique clinical feature compared with the original cases of the nasal cavity (Table 1). First, it disseminated to the bone marrow, gastrointestinal tract, skin, CNS, liver and spleen quickly. Guler et al.[8] determined that these sites were the homing parts for CD56+ lymphoma. Second, poor prognosis had been occurred, most patients died within half a year after diagnosis. Eleven of twelve cases had followed up, including 10 cases of which survived 2–12 months, the median survival time was 4.5 months with 8 cases (72.7%) died within 6 months. The survival time of all dead cases was less than 1 year. One patient survived 14 months, but finally lost to follow up. Kim et al.[4] figured that the primary testicular NK/T-cell lymphoma was a unique type of extranodal nasal type NK/T-cell lymphoma with highly aggressive. In this paper, we reported two cases, one case was lost to follow-up after discharge, another died within 4 months after diagnosis, which supported the conclusions of Kim and etc.

The cytological spectrum of extranodal NK/T-cell lymphoma was very broad. Small or small, medium and large mixed tumor cells diffuse growth with irregular nucleus could be observed, but rich prominent nucleoli were not seen. A few of eosinophils, neutrophils, plasma cells and small lymphocytes could be found in background with obvious histocyte proliferation. Coagulation necrosis accompanied by ulcer formation was present.

The neoplastic cells of nasal-type showed positive for CD2, CD3ε, EBV, CD56, cytotoxic granules (granzyme B, perforin, TIA-1) and negative for some characteristics of NK cell such as CD16 and CD57. T-cell receptor (TCR) gene mutation associated with Epstein-Barr virus infection expressed. The immunophenotype of primary testicular extranodal nasal-type NK/T-cell lymphoma is fully consistent with extranodal nasal NK/T-cell lymphoma, except for associated with EBV infection more closely (100%), TCR-γ gene rearrangement was negative (100%). Therefore, if tumor cells showed $CD2^+$, $sCD3^-$, $CD3\varepsilon^+$, EBV^+, $CD56^+$ and cytotoxic granules (granzyme B, Perforin, TIA-1)$^+$, especially $CD3\varepsilon^+$, EBV^+ and $CD56^+$ combining with morphological features will support the diagnosis of testicular extranodal nasal-type NK/T-cell lymphoma. In this paper, the two cases showed that $CD2^+$,$sCD3^-$, $CD3\varepsilon^+$, $EBER1/2^+$, $CD56^+$ and granzyme B^+, meanwhile, without other sites of lymphoma involvement except for testicles, which favor the diagnosis of primary testicular extranodal NK/T-cell lymphoma.

Primary testicular extranodal nasal-type NK/T-cell lymphoma was a kind of lymphoma expressed active for CD56 which was shown an important immunophenotype in it. But CD56 was not a unique characteristic of extranodal nasal-type NK/T-cell lymphoma, it was also expressed in other NK-cell tumors and part of peripheral T-cell lymphoma (PTCL). As the plasmacytoma was quite different from extranodal nasal-type NK/T-cell lymphoma in the histologic characteristics and immunophenotype, so it was easily identified. While the primary testicular extranodal nasal-type NK/T-cell lymphoma should be distinguished from other NK cell tumors (aggressive NK cell leukemia, blastic plasmacytoid dendritic cell neoplasm) and primary testicular non-NK/T-cell lymphoma. (1) Aggressive NK cell leukemia: It's sometimes extremely difficult to differentiate from the primary testicular extranodal NK/T-cell lymphoma. It was defined that aggressive NK cell leukemia was performance of leukemia period of extranodal nasal-type NK/T-cell lymphoma[5, 12] by WHO in 2001. The same point of extranodal nasal-type NK/T-cell lymphoma and aggressive NK cell leukemia was the same immunophenotype, TCR gene germ line expressed which was closely related with EBV infection. However, most of onset of aggressive NK cell leukemia was teenager, often

involving the peripheral blood, bone marrow, liver and spleen and etc, skin involvements were rarely found. Medium-sized cells diffuse monomorphic grew in morphology. Nakashima et al.[13] suggested that aggressive NK cell leukemia had access of 1q and lose of 7p15.1–p22.3 and 17p13.1 with method of comparative genomic studies compared with extranodal nasal-type NK/T-cell lymphoma. (2) Blastic plasmacytoid dendritic cell neoplasm: It was named "blastic NK cell lymphoma" in WHO 2001, replaced by "blastic plasmacytoid dendritic cell neoplasm" in WHO classification 2008, and was placed under the group of "Acute myeloid leukemia and related precursor neoplasms". Immunophenotype of "blastic plasmacytoid dendritic cell neoplasm was same with extranodal nasal-type NK/T-cell lymphoma. Blastic plasmacytoid dendritic cell neoplasm was occurred in adults who present with skin lesions. There were uniform characteristics in it with acute lymphoblastic leukemia and acute myeloid leukemia in histology. Tumor cells were medium size. Necrosis was rarely observed. It was not located with EBV infection. (3) Other $CD56^+$ lymphomas: Chan et al.[12] reported few cases of other $CD56^+$ lymphomas such as hepatosplenic T-cell lymphoma, $S\text{-}100^+$ T-cell lympho-proliferative disease, T chronic lymphocytic/ prolymphocytic leukemia, lymphoblast lymphoma and histiocytic lymphoma, however, expression of EBV wasn't observed in all of these cases. (4) Other primary testicular non-NK/T-cell lymphomas: Expression of CD20 was shown in B cell-derived NHL such as DLBCL without expression of sCD3 and CD3ε. Angiocentric/angiodestructive features and expression of EBV and CD56 were not found in T cell-derived NHL such as peripheral T-cell lymphoma (PTCL) and anaplastic large cell lymphoma (ALCL).

As only a few primary testicular extranodal nasal-type NK/T-cell lymphomas have been reported so far. The natural course of the disease is unclear. And the effective treatment option has not been established as for B cell testicular lymphoma (surgical resection plus chemotherapy and plus radiotherapy). Therefore, it's necessary to further collect cases to discuss its clinical and pathological features and treatments. The disease spread and recur early, the clinical course showed highly aggressive, most patients died of gastrointestinal bleeding and CNS invasion within six months, even after surgery and treated with combined chemotherapy and radiotherapy. Drenou et al.[14] considered that NK/T-cell lymphoma was related with multidrug resistance genes (MDR-1). Takenaka[15] explored high-dose chemotherapy combined with peripheral blood stem cell transplantation to 3 cases of NK/T-cell lymphoma, with 2 patients achieved complete remission. So that bone marrow or peripheral blood stem cell transplantation is likely to be effective treatment for this disease.

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