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Case Report

Intravascular NK/T-cell lymphoma in the testis: a novel case report and review of the literature

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Abstract: Intravascular NK/T-cell lymphoma (IVNKTL) is an extremely rare type of lymphoma that frequently affects the skin. To date, only 14 cases of IVNKTL have been described. To the best of our knowledge, this is the first case report of IVNKTL in the testis.

Keywords: Intravascular NK/T-cell lymphoma, lymphoma, testis, diagnosis, differential diagnosis

Introduction

Intravascular lymphoma (IVL) is a rare and aggressive form of lymphoma characterized by neoplastic cells within blood vessels, and a predilection for the skin and brain. Most cases of IVL have a B-cell phenotype, but even rarer T-cell and NK-cell variants have been described [1]. Here we first report a case of IVNKTL presenting left testis swelling and review the literature.

Case report

A 58-year-old man presented to the hospital because of 3 months history of left testis swelling without pain, fever, urgency, frequent urination and dysuria in March, 2014. Physical examination showed swelling of the left testis. The results of radiological examination including magnetic resonance imaging (MRI) of the brain, neck, thorax and abdomen were unremarkable. Bone marrow biopsy and laboratory tests demonstrated no abnormalities. Surgical excision was recommended and the patient received a resection of the left testis. Postoperative pathological diagnosis was intravascular NK/T-cell lymphoma of the left testis. The patients received three courses of combination chemotherapy consisting of cyclophosphanide, doxorubicin, vincristine, and prednisone (CHOP), and was alive with no evidence of the disease after 22 months follow-up.

Grossly, the left testis measured 7 cm × 6 cm × 5 cm with smooth surface. The cut surface was soft to firm, fleshy, and gray to white with variable areas of yellow-red discoloration. Histologically, medium-sized to large-sized pleomorphic cells were confined within vessels in the interstitial tissue of testis. The pleomorphic cells had oval nuclei and a moderate amount of cytoplasm. Many mitotic figures were observed (**Figure 1**). Immunohistochemically, the neoplastic cells were positive for CD3, CD56, TIA-1, perforin, and granzyme B (GrB), and negative for CD20, CD 79α, Pax-5, CD30, CD68, CD4, and CD8. The Ki-67 proliferation indices were approximately 100%. The vessels around the neoplastic cells were positive for CD34 and CD31, while negative for D2-40 (**Figure 2**). The intravascular neoplastic cells exhibited nuclear positivity for Epstein-Barr virus (EBER) (**Figure 3**). Overall findings supported a diagnosis of IVNKTL arising in the testis.

Discussion

IVNKTL is an extremely rare type of highly aggressive lymphoma. In 2003, Santucci [1]

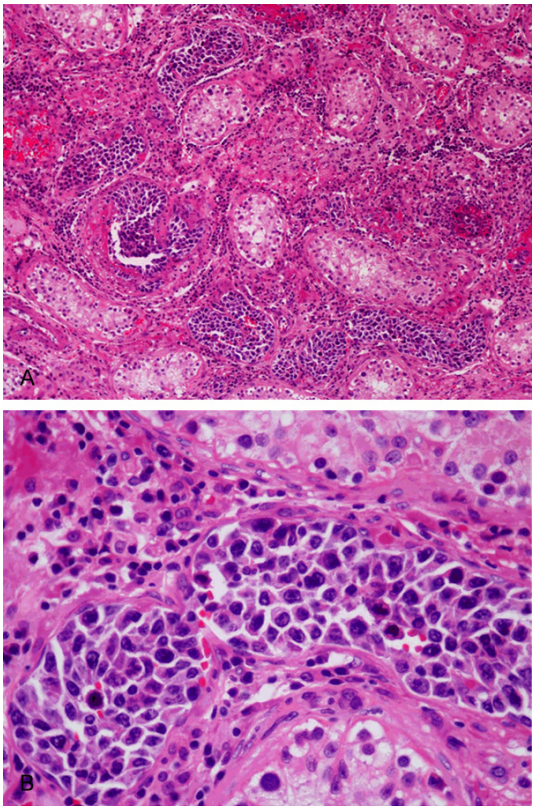

Figure 1. Microscopic findings. A: Neoplastic cells arranged within vessels located in the interstitial tissue of testis (100 ×). B: Medium-sized to large-sized pleomorphic cells were confined within vessels and mitotic figures were easily found (400 ×).

first reported one case of IVNKTL presented with erythematous plaques on the trunk and thighs, leucopenia, and weight loss. To date, only 14 cases of IVNKTL have been reported in the English literature [1-9]. The clinicopathogical features of the 15 cases including our case are summarized in **Table 1**, including 8 male and 7 female patients, with the mean age of 46.9 years old (range 18~72 years). Of the reported cases, the clinical course lasted from 2 months to 3 years, erythematous skin plaques or nodules on the trunk or limbs were observed in 14 cases, fever was observed in 5 cases, central nervous system (CNS) involvement was observed in 4 cases, and bone marrow involvement was observed in 2 cases. None of these 14 cases had nasal lymphoma. They were not related to nasal NK/T-cell lymphoma. The present patient only showed swelling of the left testis without skin or other organs involved, and to the best of our knowledge, this is the first reported case of IVNKTL confined to the testis. All 14 cases exhibited the same immunophenotype resembling that of nasal NK/T-cell lymphoma. Immunohistochemistry (IHC) showed that 14 cases were positive for CD3, CD56, and cytotoxic proteins including perforin, granzyme B and TIA-1, and negative for CD20 and CD79α. The Ki-67 proliferation indices were approximately 70-100% which denoted active proliferation of the neoplastic cells. In situ hybridization for EBER was positive in 13 cases. In our case, the immunohistochemical features and EBER in situ hybridization (ISH) results supported the diagnosis of IVNKTL. Among 14 previous reported cases, 1 case was without treatment, 2 cases of treatment was unknown, the other 11 cases were treated with CHOP or modified CHOP chemotherapy, and 2 cases among the 11 cases received stem cell transplantation (SCT) therapy meanwhile. Two cases were died at 14 and 15 days after diagnosis respectively because of the rapid progress of the disease. Eight cases were died during 4 to 17 months follow-up. Four cases were free of disease during 3 to 12 months follow-up. In the present case, the patient received three courses of CHOP chemotherapy and remained disease free after 22 months, and is undergoing follow-up.

Though extremely rare, the pathologic diagnosis of IVNKTL is often not difficult based on distinctive histopathologic, immunohistochemistry features, and EBV in situ hybridization analysis. However, IVNKTL should be distinguished from extranodal NK/T-cell lymphoma, nasal type (ENKTCL), aggressive NK-cell leukemia (ANKL), intravascular large B-cell lymphoma (IVLBCL), intravascular anaplastic large cell lymphoma (IVLBCL), and metastatic carcinoma. Main clues for diagnosis and differential diagnosis including: IVNKTL tumor cells are confined within blood vessels. The size of the tumor cells are medium to large and are similar to lymphoblastoid cells in morphology. The immunophenotype of IVNKTL is similar to that of ENKTCL in which the neoplastic cells are positive for CD56, T-lineage (e.g., CD2 and CD3) markers and cytotoxic proteins including perforin, granzyme B, and TIA-1, whereas negative for B-lineage (e.g., CD20, CD79α, and Pax-5) markers. IVNKTL showed near 100% Ki-67 expression, indicating that proliferative activity of the tumor cells is very high. In situ hybridization for EBER is usually positive. It is needed to

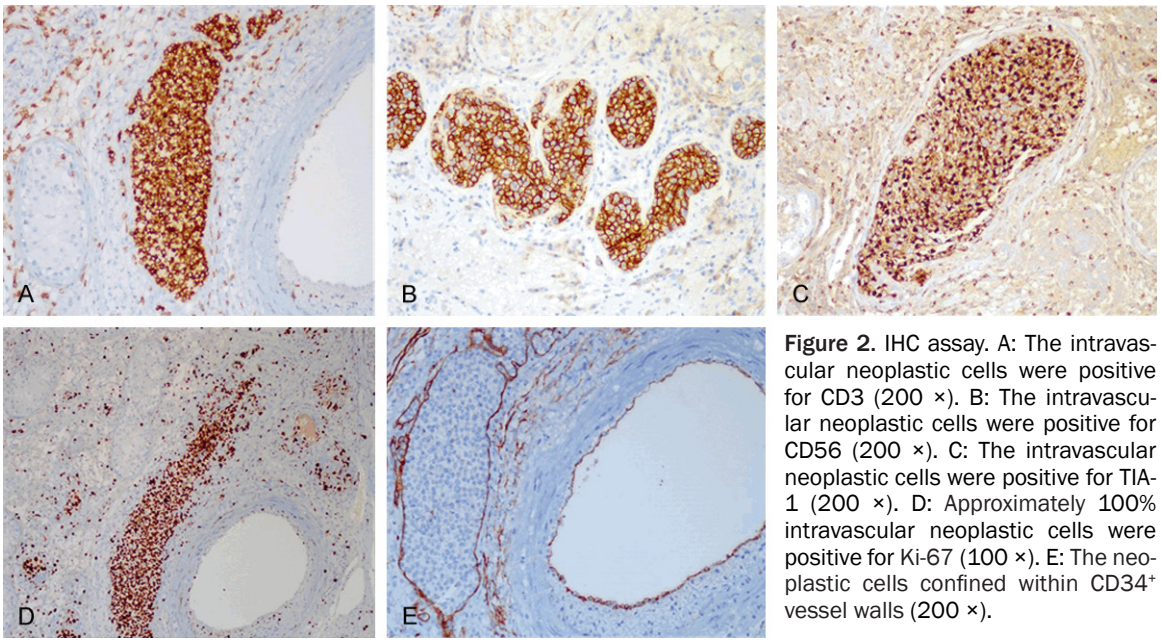

Figure 2. IHC assay. A: The intravascular neoplastic cells were positive for CD3 (200 ×). B: The intravascular neoplastic cells were positive for CD56 (200 ×). C: The intravascular neoplastic cells were positive for TIA-1 (200 ×). D: Approximately 100% intravascular neoplastic cells were positive for Ki-67 (100 ×). E: The neoplastic cells confined within $CD34^+$ vessel walls (200 ×).

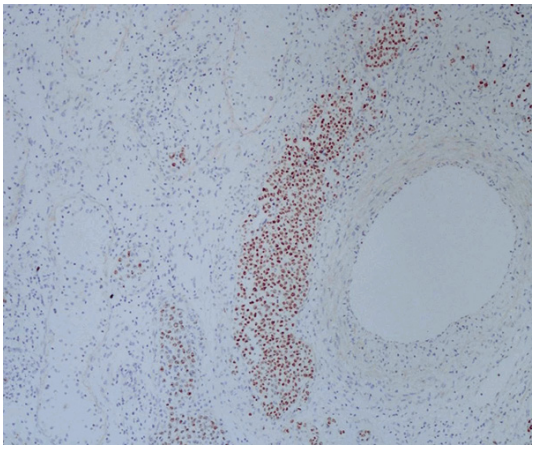

Figure 3. ISH assay. The intravascular neoplastic cells were universally EBV positive as determined using ISH.

pay special attention, IVNKTL should be distinguished from ANKL because of the similar histopathologic appearance, immunophenotype and infection with EBV. The features of IVNKTL and ANKL may overlap during the course of disease, which may represent different disease status [8]. Erythematous, plaque-like skin lesions or rash are typically prominent in most IVNKTL patients whereas usually without obvious abnormalities in the peripheral blood, although bone marrow involving might be present in some patients. In ANKL, tumor cells are diffusely scattered in the extravascular tissue rather than strictly confined within blood vessels, which is different from IVNKTL.

In summary, IVNKTL is an extremely rare, highly aggressive and EBV-associated lymphoma with a poor prognosis as a whole, which may be mainly due to multiorgan and multisystem involvement. The treatment of this disease is mainly based on CHOP or modified CHOP regimen, but the curative effect is far from satisfaction. In the present case, the tumor only involved the left testis without multiorgan or multisystem involvement. The patient received three courses of CHOP chemotherapy after surgery, and is remaining disease free for 22 months. However, the long-term prognosis of the patient remains to be further followed up and more cases should be documented for further understanding of this peculiar rare type of lymphoma and developing new effective methods for its treatment.

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Disclosure of conflict interest

None.

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Table 1. Clinicopathogical features of 15 cases of Intravascular NK/T-cell lymphoma

Reference	Age/ Sex	Clinical features	IHC		EBER	Treatment	Follow-up
			Positive	Negative			
[1]	54/M	Erythematous plaques on trunk and thighs	CD3ε, CD56, TIA-1, GrB, CD30, Ki-67 (100%)	LMP1, CD4, CD8, CD20, CD79α, CD57, CD68, bcl-2	+	Five CHOP courses	17-month died of CNS involvement
[2]	41/M	Erythematous plaques on lower extremities	CD3ε, CD56, CD2, CD7, CD43, Bcl-2, TIA-1, Perforin	CD20, CD30, CD5, CD4, lysozyme, myeloperoxidase, CK	+	CHOP and SCT	12-month free of disease
[2]	47/F	Myalgia, arthralgia, weakness, fever, confusion, pancytopenia	CD2, CD3ε, CD7, CD56, TIA-1, GrB	CD20, CD4, CD5, CD8, CD57	-	Unknown	15-day died of multiple organ involvement including CNS
[3]	71/F	Erythematous nodules and patches on trunk and extremities	CD3ε, CD56, TIA-1, Ki-67 (99%)	CD20, CD4, CD5, CD8, CD10, CD30, bcl-6, LMP-1	+	No treatment	Alive 5-month after diagnosis
[4]	40/F	Erythematous skin lesions on whole body	LCA, CD3, CD56, TIA-1, GrB, CD45, Ki-67 (100%)	CD20, CD4, CD8, CD29	+	CODOX-M/IVAC	7-month free of disease
[5]	23/F	Abdomen erythema, leg edema, ileal ulcer, splenomegaly, fever	CD3ε, CD56, TIA-1, Ki-67 (100%)	CD20, CD79α, CD45RO	+	CHOP, ProMACE/CytaBOM, L-ASP/CY, hyper CVAD/MTX-Arac, related SCT	9-month died of aGVHD
[6]	63/M	Red-violaceous plaques on trunk and extremities	CD3ε, CD2, CD45RO, CD56, TIA-1	CD20, CD4, CD5, CD8, CD7	+	3 cycles of CHOP	6-month died after diagnosis
[7]	72/M	Erythematous plaques on trunk and extremities, secondary involvement of bone marrow and CNS	CD3ε, CD56, TIA-1, Ki-67 (70%)	CD20, CD4, CD29, CD8, CD30, CD34, CD54, MPO, Pankeratin	+	3 cycles of chlorambucil+urbasone	7-month died of spsis
[8]	38/F	chest and back erythema, fever	CD3, GrB, CD56, Ki-67 (90%)	CD4, CD5, CD8, CD20, CD30, Pax-5, TdT	+	5 cycles of CHOP	13-month died of CNS involvement
[9]	45/M	Red macules on turnk and thigh	CD2, CD3ε, CD56, TIA-1 GrB, Perforin, Ki-67 (90-100%)	CD4, CD8, CD20, CD30	+	Unclear	2-week died of disease
[9]	52/F	Subcutaneous nodules in the left parotid region	CD2, CD3ε, CD56, TIA-1 GrB, Perforin, Ki-67 (90-100%)	CD4, CD8, CD20, CD30	+	6 cycles of CHOP	6-month died of disease
[9]	32/M	Patches on left thigh, fever	CD2, CD3ε, CD56, TIA-1 GrB, Perforin, Ki-67 (90-100%)	CD4, CD8, CD20, CD30	+	1 cycle of CHOP	4-month died of disease
[9]	18/F	Red macules and plaques on lower legs accompanying pain	CD2, CD3ε, CD56, TIA-1 GrB, Perforin, Ki-67 (90-100%)	CD4, CD8, CD20	+	CHOP	36-month free of disease
[9]	51/M	Abdominal pain and red patches on turnk and thigh, fever	CD2, CD3ε, CD56, TIA-1 GrB, Perforin, Ki-67 (90-100%)	CD4, CD8, CD20, CD30	+	CHOP+VP-16	6-month died of disease
Our case	57/M	Enlargement of left testis	CD3, CD56, TIA-1 GrB, Perforin, Ki-67 (approximately 100%)	CD20, CD79α, Pax-5, CD30, CD68, CD4, CD8	+	3 cycles of CHOP	22-month free of disease

CNS, Central nervous system; SCT, Stem cell transplantation; CODOX-M, Cyclophosphamide, vincristine, doxorubicin and methotrexate; VAC, Ifosfamide, mesna, etoposide and cytarabine; ProMACE/CytaBOM, Prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytosine arabinoside, bleomycin, vincristine, leucovorin; L-ASP, L-asparaginase; CY, Cyclophosphamide; hyper CVAD, Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; MTX, Methotrexate; AraC, Cytosine arabinoside; aGVHD, Acute graft-versus-host disease.

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