

Case Study

ALK-positive Anaplastic Large Cell Lymphoma presenting as a solitary bladder neoplasm: A case report and review of the literature

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Abstract: Anaplastic large-cell lymphoma (ALCL) with involvement of the urinary bladder is rare. We report a unique case of ALK-positive ALCL in a 17-year-old male patient. He presented with dysuria for three months and gross hematuria for one month. The computed tomography scan and the cystoscopy revealed a single broad-based lesion measuring 3x2 cm on the right lateral wall of the urinary bladder. There was no lymphadenopathy and no tumor outside of the bladder. Biopsy of the lesion showed diffuse large pleomorphic cells infiltrating the lamina propria and strongly expressing CD30, ALK, and T-cell markers. A clonal TCR-gamma gene rearrangement was detected by PCR and ALK gene rearrangement was observed by fluorescence in situ hybridization. The patient was not treated and remains asymptomatic 6 months after the diagnosis. This is the eleventh documented instance of ALCL involving the bladder and the second reported cases of localized primary bladder ALK-positive ALCL.

Keywords: Anaplastic large-cell lymphoma, Anaplastic lymphoma kinase, Bladder

Introduction

Anaplastic large-cell lymphoma (ALCL) is characterized by diffuse expression of CD30 by the neoplastic T-cells. It is further classified as primary cutaneous ALCL and systemic ALCL based on the sites of involvement. Anaplastic lymphoma kinase (ALK) is negative in cutaneous ALCL, whereas systemic ALCL can be ALK-positive or ALK-negative. The patients with cutaneous ALCL commonly present with solitary or localized skin nodules in the trunk, face, extremities and buttocks. Systemic ALCL involves

lymph node and extranodal sites, and the frequent extranodal sites include skin, bone, and soft tissues [1].

ALK-positive and ALK-negative ALCL account for approximately 3% and 2.5% of non-Hodgkin lymphoma, respectively [2]. The former frequently occurs in the first three decades of life with a male predominance (M:F ratio = 1.7:1) [3–5]. In contrast, ALK-negative ALCL usually affect the elderly (median age of 58 years) and also show a male predominance (M:F ratio = 1.5:1) [5].

Primary lymphoma of the bladder is uncommon. Primary ALK-positive ALCL of the bladder is extremely rare. Here, we report a unique case of ALK-positive ALCL presenting as a solitary bladder lesion

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in a young adult.

Case Report

A 17-year-old previously healthy man presented with dysuria for three months and gross hematuria for one month. He denied fever, night sweats, or weight loss. A computed tomography (CT) scan showed an irregular thickening of the right lateral wall of the bladder. No other lesions or lymphadenopathy were observed. The patient underwent cystoscopy, which revealed a broad-based lesion measuring 3x2 cm on the right lateral wall of the bladder. A transurethral excision of the lesion was done and the excisional biopsy was sent for histology.

The specimen was fixed in formalin and embedded in paraffin. Microscopically, there were diffuse infiltrates in the lamina propria and the infiltrates were composed of sheets of large pleomorphic cells [Figure 1A, B]. The large cells had abundant eosinophilic cytoplasm, eccentric nuclei with irregular nuclear contours, and prominent nucleoli. Some had reniform or horseshoe-shaped nuclei. Mitoses were frequent [Figure 1B]. A background of small lymphocytes and eosinophils was also present. The urothelial mucosa was intact and unremarkable.

The tumor cells were positive for CD45, CD2, CD4, CD30 (diffuse and strong) [Figure 1C], ALK (nuclear and cytoplasmic) [Figure 1D], EMA and granzyme B, and negative for CD20 and CD3. Ki67 showed a proliferative index of 40%. The morphologic and immunophenotypic findings supported the diagnosis of ALK-positive ALCL.

Fluorescence in situ hybridization (FISH) using a break-apart probe for the ALK gene (Guangzhou Anbiping Limited Liability Company) identified ALK gene rearrangement in 20% of the cells [Figure 1E]. Genomic DNA was also extracted from paraffin-embedded tissue and a T cell receptor (TCR)-gamma gene rearrangement by PCR (BIOMED II primers) was done. A clonal TCR-gamma gene rearrangement was detected [Figure 1F]. Both results further

supported the diagnosis of ALK-positive ALCL.

The patient was not treated and remained asymptomatic 6 months after the diagnosis.

Discussion

Lymphoma with primary involvement of the bladder is uncommon and comprises approximately 0.2% of all bladder neoplasms [16]. Primary bladder lymphoma was first described by Eve in 1885 [17]. Extranodal marginal zone lymphoma of mucosa associated lymphoid tissues and diffuse large B-cell lymphoma (DLBCL) are the two most common types.

ALCL with involvement of the urinary bladder is extremely rare and only 11 cases have been reported [6–15]. The clinicopathologic features and outcome of the reported cases as well as our case are summarized in Table 1. Ten of eleven cases (91%) are ALK-positive ALCL, and only one case (case 11) (9%) is ALK-negative ALCL. The median age of ALK-positive ALCL is 27.5 years (ranging from 17 to 78 years). It occurs almost all in male with one exception. The majority of the cases (80%, 8 of 11) involve multiple sites in addition to the bladder. Two patients (case 2 and our case) presented with a localized bladder tumor. The average follow-up time is 10 months (ranging from 1 to 84 months). Seven patients achieved complete remission after chemotherapy and/or surgical excision. Two patients did not achieve remission and expired one month and six months after diagnosis, respectively. The patient with ALK-negative ALCL did not respond to the chemotherapy and died nine months after the initial diagnosis.

The diagnosis of ALCL in bladder is challenging due to the rarity of the entity and a long list of differential diagnosis of large pleomorphic neoplastic cells. The list includes undifferentiated urothelial carcinoma, metastatic carcinoma, sarcoma, melanoma, ALK-positive DLBCL, and inflammatory myofibroblastic tumor. In addition to morphology, immunohistochemical workup is essential to render a correct diagnosis. Undifferentiated urothelial carcinomas

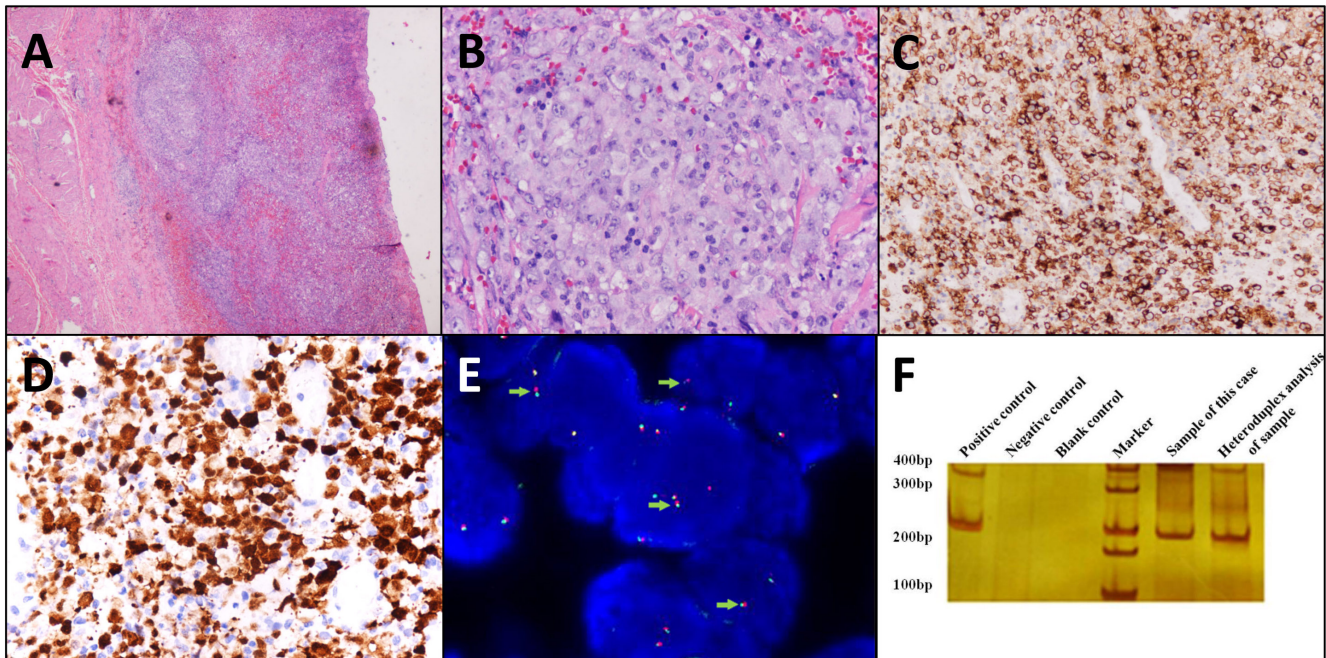


Figure 1: ALK positive Anaplastic Large Cell Lymphoma of the bladder. A. The H&E section shows a diffuse lymphoid infiltrate in the lamina propria (40). B. The tumor cells are large, pleomorphic with prominent nucleoli (400X). C. The tumor cells are positive for CD30 (400X). D. The tumor cells are positive for ALK with both nuclear and cytoplasmic staining (400X). E. The 5' end of the probe for ALK gene is labeled with Spectrum Green and the 3' end is labeled with Spectrum Orange. The split red and green signals indicate ALK gene rearrangement (arrows). F. A clonal TCR-gamma gene rearrangement is detected by PCR (see the band at 220bp).

and metastatic carcinoma are commonly positive for cytokeratin without expression of T-cell markers, CD30 and ALK. Both ALK-positive DLBCL and inflammatory myofibroblastic tumor can be positive for ALK. However, ALK-positive DLBCL originates from B cell with plasma cell differentiation and tumor cells are positive for plasma cell markers CD138, but usually negative for CD30 and T-cell markers. The ALK immunostaining in ALK-positive DLBCL shows a characteristic granular cytoplasmic staining pattern, which is different from the nuclear and diffuse cytoplasmic staining pattern commonly seen in ALK-positive ALCL. Inflammatory myofibroblastic tumor shows spindle cell proliferation admixed with lymphocytes, plasma cells and eosinophils, and tumor cells are often positive for smooth muscle actin.

Our case is an example of early stage ALK positive ALCL presenting with a single superficial bladder lesion. Though rare, it is important to add this entity in the differential for large pleomorphic proliferation of the bladder, especially if the other markers (cytokeratin, CD20, CD3, etc) are negative. CD30 immunostaining should be included in the workup. A correct diagnosis of ALCL can be made with the typical hallmark cell morphology and an appropriate immunohistochemical panel with supportive clonal TCR rearrangement and FISH findings [1, 2, 18, 19].

Based on the studies, the treatment for ALCLs in bladder, systematic chemotherapy is the main treatment besides surgical excision combines with chemotherapy is an effective treatment used for diseases at early stage. Eight of eleven cases (73%) underwent chemotherapy. Six of eight were treated

Table 1: Clinicopathologic features of 11 cases of anaplastic large cell lymphoma involving the bladder

Patient	Age/sex	Presentations	Sites involved	ALK (IHC/FISH)	TCR	Therapy / Response	Re-	Follow-up (mth)
1 ^[6]	22/M	Multisystemic symptoms	Bladder, hepatosplenomegaly, diffuse LAD	+ /ND	ND	CHOP x6 / CR		Alive (33)
2 ^[7]	27/M	Hematuria, left iliac fossa pain	Bladder	+ /ND	ND	Surgery, CHOP x4 / CR		Alive (84)
3 ^[8]	78/F	Fever and lumbar pain, acute respiratory failure	Bladder, bronchus and trachea	+ /ND	ND	NA/NA		Alive (NA)
4 ^[9]	28/M	Abdominal pain, dysuria, and gross hematuria.	Bladder; diffuse LAD	+ /ND	ND	CHOP x6 / CR		Alive (12)
5 ^[11]	26/M	Back pain, hematuria, weight loss, and night sweats	Prostate, bladder neck, trigone, left ureteric orifice, diffuse LAD, multiple pulmonary nodules, and a large lytic defect in the left innominate bone	+ /ND	ND	CHOP / CR		Alive (NA)
6 ^[11]	45/M	Back pain, hydronephrosis	Bladder, diffuse LAD	+ /ND	+	etoposide, irinotecan, cytarabine, and methylprednisolone / CR		Alive (4)
7 ^[12]	51/M	liver transplant, PTL	Bladder, abdominopelvic LAD	+ /ND	+	R-CHOP x4 / NR		Died (6)
8 ^[13]	22/M	Back pain, bladder mass, hydronephrosis	Bladder	+ /ND	ND	CHOP x4 / CR		Alive (8)
9 ^[14]	59/M	Adult onset Still's Disease, hemophagocytic syndrome	Bladder, mesenteric, diffuse LAD	+ /ND	ND	Anti-inflammatory therapy / NR		Died (1)
10	17/M	Dysuria and gross hematuria	Bladder	+ /+	+	Surgery / CR		Alive (6)
11 ^[15]	39/M	Acute renal failure, bilateral ureteral obstruction, HIV	Pelvic mass involving the bladder	- /ND	ND	Aggressive chemotherapy / NR		Died (9)

Abbreviations: ALK, anaplastic lymphoma kinase; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete remission; LAD, lymphadenopathy; mth, months; NA, not available; ND, not done; NR, no remission; PR, partial remission; R-CHOP, rituximab plus CHOP; TCR, T-cell receptor γ ; +, positive; -, negative.

using the CHOP regime. Five of eight (63%) with follow-up data were alive and well [6–15]. Our case only has surgical excision without chemotherapy, however, he is still alive and without relapse, the key factor was that the single localized lesions at early stage, and entirely surgical resection can achieve better effect.

Acknowledgements

This work was supported by the Chongqing Foundation Frontier Research Plan Project (Grant No. cstc2013jcyjA10003). The authors claim no conflicts of interest.

Received: July 9, 2016 **Accepted:** October 5, 2016

Published: October 20, 2016

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