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Anaplastic Large Cell Lymphoma Involving the Bladder: Rare Involvement of a Rare Malignancy

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Abstract

Anaplastic large cell lymphoma (ALCL) is a rare and unfortunately aggressive lymphohematopoietic malignancy. While it can affect a number of extranodal sites, genitourinary involvement is extremely uncommon, with only eleven reported cases in the literature. Here, we report a case study of a healthy 50-year-old male with no prior urologic history, presenting with chief complaint of gross hematuria. Non-contrast CT imaging demonstrated irregular contours within the bladder with mild hydronephrosis bilaterally, regional lymphadenopathy, and a lytic bone lesion, concerning for malignancy. The patient was taken for cystoscopy, and biopsies were obtained from what was immediately apparent to be a grossly invasive tumor. His hospital course was further complicated by acute-on-chronic renal failure in the setting of stable, non-obstructing hydronephrosis, requiring placement of bilateral nephrostomy tubes. Ultimately, a pathologic diagnosis of anaplastic lymphoma kinase (ALK)-negative ALCL was made, which is notably one of eleven cases of ALCL with primary bladder involvement and only the second of these cases that is ALK-negative.

Keywords: Anaplastic; Lymphoma; Bladder; Malignancy

Introduction

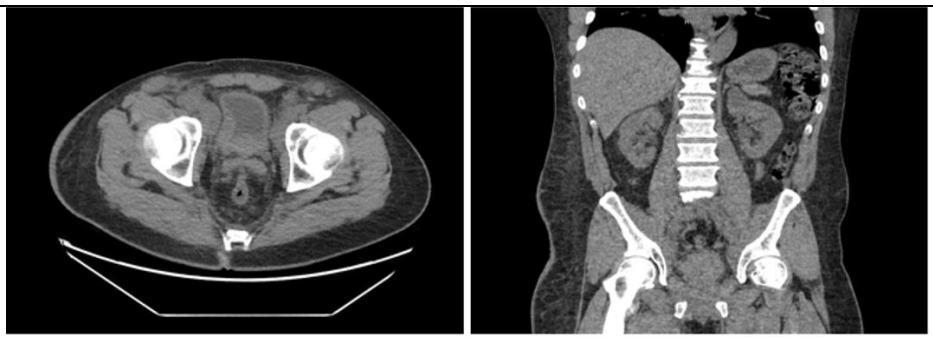
ALCL is a malignant disease on the spectrum of Non-Hodgkin's lymphoma characterized by over-expression of the T-cell marker CD30. Patients may typically present with signs and symptoms commonly associated with lymphoma, including lymphadenopathy, fevers, and weight loss [1]. However, primary malignancy or extension to genitourinary organs has been reported in a small cohort of individuals presenting with a routine urologic complaint such as gross hematuria. Throughout this discussion, we will examine the clinical relevance of ALCL and compare and contrast our case to the patients of prior published

works. We will also highlight the critical role of immunohistochemical staining in establishing the correct diagnosis, as well as the existing therapeutic options and emerging clinical trials, in hopes for a better understanding of this rare clinical entity.

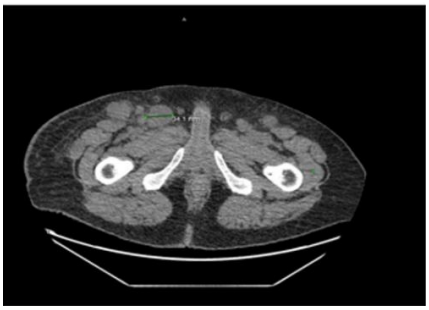
Case Report

A 50-year-old African American male presented to the emergency department with chief complaint of painless gross hematuria of one day's duration. The patient did endorse one episode of hematuria without clots five years ago which resolved spontaneously, and he did not seek medical attention at that time. Otherwise, the patient denied other relevant urologic history including dysuria, frequency, urgency, flank or suprapubic pain, as well as no recent fevers, chills, weight loss, or night sweats. His only past medical history was chronic kidney disease with a remote baseline creatinine of 1.6 mg/dL, and lifetime non-smoker. Initial workup revealed acute kidney injury with a creatinine of 2.9 mg/dL, and the patient's urinalysis was notable for packed red blood cells, pyuria, and 2+ bacteria, but negative for nitrites and leukocyte esterase.

CT abdomen/pelvis without contrast demonstrated an irregular, lobular thickening of the right and posterior bladder with mild ureteral prominence and hydronephrosis. There was also inguinal and retroperitoneal adenopathy identified, as well as a 1.5 cm lytic lesion of the L2 vertebrae (Figure 1). Given the concern of primary bladder neoplasm with metastatic spread, the patient was scheduled for cystoscopy on hospital day 3. At the time of cystoscopic evaluation, a large bladder tumor composed of friable tissue was identified. Invasion was suspected by appearance alone, and the ureteral orifices could not be appreciated. Two biopsy specimens were obtained and delivered to pathology for histologic diagnosis, hemostasis was achieved with electro-cautery, and hematology/oncology was consulted for future management recommendations.



(A) (B)



(C)

Figure 1: (A): Irregular, lobular thickening of right and posterior bladder wall with prominence of ureters; (B): Mild hydronephrosis on coronal slice, suggestive of some degree of obstructive uropathy. Unable to clarify delineate retroperitoneal lymphadenopathy on axial or coronal slices; (C): Inguinal adenopathy, largest node measuring 3.4 cm on right. Imaging suggestive of bladder neoplasm with metastatic lymphadenopathy and osseous involvement.

The patient's creatinine at the time of cystoscopy on day 3 also remained elevated at 2.8 mg/dL, and subsequently continued to rise. After reaching an apex of 5.6 mg/dL on day 6, the patient underwent repeat imaging with retroperitoneal ultrasound which yielded unchanged right and left mild hydronephrosis from the prior CT. With the worsening creatinine and relatively unimpressive hydronephrosis, although originally postulated to be medico-renal in origin versus an obstructive cause, the decision was made to place bilateral nephrostomy tubes on hospital day 7. Urine output markedly improved following the procedure, and the patient's creatinine recovered, reaching a nadir of 2.0 mg/dL on hospital day 13.

On hospital day 14, a final pathologic diagnosis of a poorly differentiated malignancy consistent with ALK-negative ALCL was established. Its small-to-medium sized cell population was noted to have irregular, multilobate nuclei with high mitotic activity and variable cytoplasm, and the tumor was infiltrative into the fibromuscular soft tissue and vessels deep to the urothelium. Immunohistochemical analysis demonstrated positivity for CD30 and CD4, while also demonstrating pankeratin (CK5/6, CK20, CK-HMW), p63, S-100, CD20, PAX5, CD15, desmin, CD3 and CD5 negativity (Figure 2).

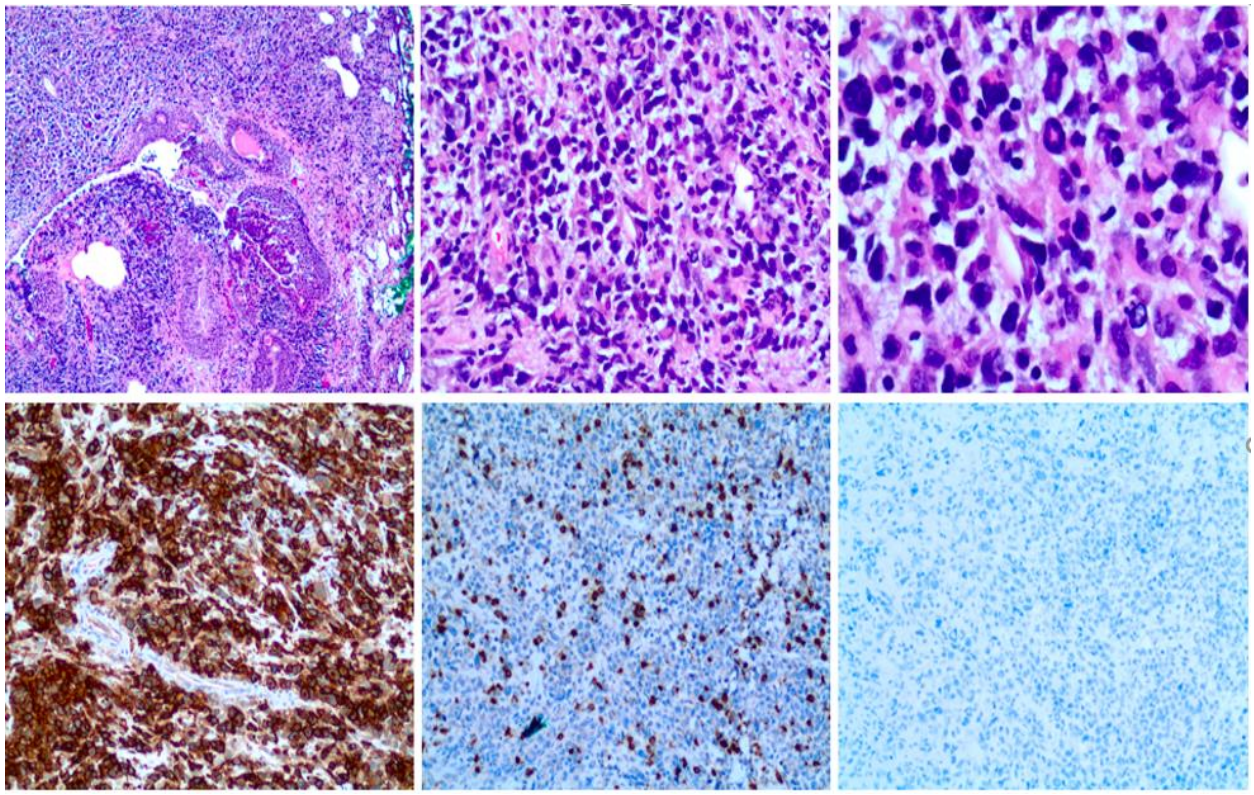


Figure 2: Anaplastic large cell lymphoma. (A): Tumor and normal urothelium, 4× magnification; (B): Tumor, 20× magnification; (C): Tumor, 40× magnification; (D): Tumor, CD30 positive; (E): CD3 stained T-cell and tumor cells (unstained); (F): All other negative stains.

Hematology/oncology recommended pharmacologic management with CHOP-E every three weeks for six cycles. The patient then underwent placement of a peripherally inserted central catheter as well as a baseline 2D echocardiogram given the cardiotoxicity associated with anthracycline-based chemotherapy, and was discharged home the same day with indwelling

nephrostomy tubes. Two weeks following discharge, the patient's case was presented at a multidisciplinary tumor board. Given poor outcome of ALK negative ALCL he was recommended for a clinical trial with brentuximab vedotin and CHEP (BV-CHEP).

Discussion

ALCL is a rare variant of Non-Hodgkin's lymphoma characterized by diffuse CD30 expression in neoplastic T-cells. As a poorly differentiated neoplasm, it is often detected as stage III or IV advanced disease involving bone and extranodal sites at time of presentation [1]. ALCL is classified by the World Health Organization into two subgroups determined by its ALK status. ALK-positive disease typically affects young individuals, with a slight male predominance, in the first three decades of life, and carries with it a good prognosis and favorable response to treatment. The (2;5) (p23;q35) translocation is well-known to be the culprit implicated in its pathogenesis, a genetic event that creates a nucleophosmin (NMP)-ALK fusion protein, which upregulates a receptor tyrosine kinase (RTK) that promotes both cellular proliferation and anti-apoptotic mechanisms. Conversely, ALK-negative ALCL tends to involve older patients, with a mean age of 58 years and similar slight male predominance, and entails a much poorer prognosis. ALCL can be further categorized into cutaneous (cALCL) and systemic varieties, with the former being constitutively ALK-negative with nodule formation on the trunk, face, and extremities, and the latter being variable in ALK status with involvement of skin, bones and soft tissue [2,3].

Compared to its ALK-positive counterpart, the major oncogenic driver of ALK-negative disease is less well understood, with translocations involving DUSP22, a phosphatase involved in T-cell receptor signaling, mutations of the RTK JAK/STAT, and rearrangements of TP63 being identified in 30%, 20%, and 8% of cases. More recently, in an article published in Blood in 2016, Scarfo et al. investigated the role of ERBB4. This RTK, a member of the ERBB family shared by EGFR (ERBB1) and HER2 (ERBB2) of lung and breast cancer respectively, was identified in 24% of ALK-negative cases, an exclusive finding as it was undetectable in its ALK-positive equivalent. Interestingly, treatment with the HER2 monoclonal antibody neratinib in xenograft models also demonstrated a reduction in tumor growth, a possible catalyst for future clinical trials [4].

Lymphoma presenting as a bladder cancer represents only 0.2% of all bladder neoplasms, and of those, mucosa-associated lymphoid tissue (MALT) lymphoma and diffuse large B-cell lymphoma (DLBCL), cancers of B-cell origin, are the two most commonly cited [3]. Therefore, T-cell ALCL with urinary tract involvement is exceedingly rare, with a review of the current literature revealing only eleven documented cases. Of this small patient population, all were male except one, with a mean age of 40 years. Ten patients presented with ALK-positive disease, interestingly the only ALK-negative patient was noted to be HIV-positive. The most common presenting symptoms was gross hematuria, while others presented with a clinical picture of obstructive uropathy, irritative voiding symptoms, scrotal swelling, progressive low back pain, and systemic B symptoms such as fevers, night sweats, and weight loss classically associated with Non-Hodgkin's lymphoma. Multiple site involvement, including diffuse lymphadenopathy, pulmonary metastases, hepatosplenomegaly, and lytic bone defects was detected in eight cases, while only two patients presented with localized bladder tumor [1-3].

The diagnosis of ALCL is a challenging one, not only due to its rarity, but also because of the vast differential of bladder cancers. Therefore, immunohistochemical staining is critical in arriving at the correct diagnosis and excluding other rare causes. Carcinomas, such as urothelial cell (UCC), will stain positive for cytokeratins. These include high-molecular weight cytokeratin

(CK-HMW), CK5/6, which has been implicated as an independent prognostic marker in UCC, and CK20, found in full-thickness staining in urothelial carcinoma in situ. They will also be negative for the previously described T-cell marker CD30, and ALK negative [3,5-7]. While ALK-positive DLBCL and Hodgkin's lymphoma are also possibilities, they are tumors of B-cell origin, and will expectedly stain positive for markers of B-cell lineage such as CD20, PAX5, and CD15, while being negative for CD30 [2,8]. Metastatic melanoma will stain positive for S-100 and HMB-45, and inflammatory myofibroblastic tumors and embryonal rhabdomyosarcoma will stain positive for markers of myxoid differentiation such as desmin and smooth muscle actin although their ALK status may vary [2]. As demonstrated, our patient's negative stains effectively rule out other possible etiologies of an unknown bladder mass. Intriguingly, his p63 negativity may also suggest bladder cancer invasion into the prostatic stroma. Marker p63 is expressed in prostatic basal cells, and the vast majority of disruptions of the basement membrane occur in those cells lacking expression compared to the thicker and more uniform membrane of p63-positive cells [9].

Histologic examination may also provide insight towards an accurate diagnosis. While ALCL and UCC may appear similarly with a pleomorphic cell type, increased mitoses and nuclear atypia, advanced or high-grade UCC may be diagnosed by the additional finding of keratinization and intercellular bridges suggestive of squamous differentiation. Alternatively, DLBCL will exhibit a granular cytoplasmic stain while the cytoplasm of ALCL will stain diffusely. Finally, spindle cell proliferation will be the primary discovery in inflammatory myofibroblastic tumor with admixed immune cells found secondarily [3].

Treatment of ALCL centers around chemotherapy, in particular cyclophosphamide, hydroxydaunorubicin, vincristine (Oncovin), and prednisone, otherwise known as CHOP [10]. Of all seven patients who achieved complete remission, all but two received varying cycle lengths of CHOP. One 27-year-old male underwent surgery with adjuvant CHOP, while another 17-year-old male underwent surgery alone. These patients were notably the only two presenting with localized disease, making it presumable that surgery was pursued not only because of the extent of disease but also because of better overall health status. Another 45-year-old patient received therapy with ESHAP consisting of etoposide, Solu-Medrol, high-dose Ara-C (cytarabine) and cisplatin, or Platinol. Three patients did not achieve remission, and were deceased at one, six, and nine months following diagnosis and administration of anti-inflammatory therapy, rituximab plus CHOP (R-CHOP), and non-descript aggressive chemo, respectively. This included failure of response by the sole ALK-negative patient, which reinforces the poor prognosis lent by the absence of ALK expression [1-3]. The addition of etoposide to the gold standard CHOP regimen, and whether it provides survival benefit in lymphoma patients, has also been a topic of recent discussion. In a population-based cohort published in British Journal of Haematology in 2017, Cederleuf et al. analyzed 122 patients from the Danish and Swedish lymphoma registries from 2000 to 2010. Similar to the patients previously described, the median age was 40 years old, ranging from 18 to 85, with a male predominance. The five-year overall survival and progression free survival was 78% and 64% respectively. Following age stratification, comparison of CHOP-E versus CHOP regimens demonstrated an improved overall survival in the 41-65-year-old group with CHOP-E per Kaplan-Meier analysis, with a clinically significant result ($p=0.047$). In contrast, overall survival in the 18-40-year-old group surprisingly decreased with addition of etoposide [11]. Introduction of etoposide, not incorporated to CHOP in any of the eleven previous cases, may therefore be of benefit to the patient of interest in our case.

Lastly, the antibody-drug conjugate brentuximab vedotin (BV) underwent recent investigation as an adjunct treatment option for ALCL. Brentuximab binds to the CD30 receptor of neoplastic T-cells and, once internalized, releases the active chemotherapeutic agent monomethyl auristatin E, or MMAE. MMAE subsequently functions as a microtubule inhibitor, arresting the cell cycle in S phase with subsequent cell death. The drug further exerts its anti-cancer effects by promoting

antibody-dependent cellular cytotoxicity, as immune cells respond to antibody bound to CD30. 58 patients with relapsed or refractory ALCL treated with single agent BV were followed in a phase II clinical trial in an article published by Pro et al. in Blood in 2017. Outcome measures included lengths of remission, overall survival, and progression free survival. Per their analysis of five-year results, while median OS was not reached, disease progression was not noted beyond 40 months, and the most common adverse effect of peripheral neuropathy, endorsed by 33 patients, was resolved or improved at last follow-up, supporting its use as a potentially curable agent [12]. Another study actively in phase II clinical trial is investigating BV-CHEP induction therapy for CD30-positive lymphomas, with forty current participants and an estimated completion date in December of 2019. Requirements for eligibility include histologic and immunohistochemical confirmation of disease, measurable disease on PET/CT, and select labs, including adequate blood counts, renal function, and left ventricular ejection fraction. Alternatively, while active infectious diseases, cardiac disease, and prior systemic anti-lymphoma therapies may exclude patients, one prior cycle of CHOP-like chemotherapy does not qualify as prior treatment, and patients such as ours could maintain their eligibility should post-CHOP testing show inadequate responses [13].

Conclusion

Although genitourinary ALCL is a rare clinical entity, clinicians must be mindful of this possibility in keeping a broad differential diagnosis of an unknown bladder mass. This case and overview highlight the epidemiology, classification, diagnosis and treatment of this disease, and significant advances in research have been made with presumably more to follow. Regular surveillance of suspicious bladder lesions, continued investigation into its pathogenesis, and future advances in staining techniques to include reliable antibodies for ERBB4 or its end product MMP9 for ALK-negative disease may lead to earlier detection of a malignancy so often detected in advanced stages. Furthermore, continued analysis of treatment outcomes for both established chemotherapeutics and developing targeted immunotherapies may offer patients a chance of either a cure or increased longevity.

REFERENCES

1. Lawrenz J, Tomal J, Towne J. ALK+ Anaplastic large cell lymphoma with bladder involvement presenting as fever of unknown origin: A case report and literature review. World J Oncol 2013; 4: 95-101.
2. Liang X, Wang Y, Zhang J. Anaplastic lymphoma kinase-positive anaplstic large-cell lymphoma with involvement of the urinary bladder: A case report and review of literature. Onco Targets Ther 2015; 8: 1143-1147.
3. Huang Y, Yuan J, He H. ALK-positive anaplastic large cell lymphoma presenting as a solitary bladder neoplasm: A case report and review of the literature. Hematopathology. 2016; 1: 102-107.
4. Scarfo I, Pellegrino E, Mereu E, et al. Identification of a new subclass of ALK-negative ALCL expressing aberrant levels of ERBB4 transcripts. Blood. 2016; 127: 221-232.
5. Fisher JD, Pacha T, Santucci RA. Urology In-Service and board review: The essential and concise study guide. Corpus Christi. 2013; 8-9.
6. Hashmi AA, Hussain ZF, Irfan M, et al. Cytokeratin 5/6 expression in bladder cancer: association with clinicopathologic parameters and prognosis. BMC Res Notes 2018; 11: 207.
7. Arias-Stella JA, Shah AB, Gupta NS, et al. CK20 and p53 immunohistochemical staining patterns in urinary bladder specimens with equivocal atypia. Arch Pathol Lab Med 2018; 142: 64-69.
8. Pernick MD N. CD Markers: CD15, Retrieved from Pathology Outlines. 2018.

9. Liu A, Wei L, Gardner WA. Correlated alterations in prostate basal cell layer and basement membrane. Int J Biol Sci 2009; 5: 276-285.
10. Cheson BD, Leonard JP. NonHodgkin Lymphoma: New drug combinations. Retrieved from Medscape. 2018.
11. Cederleuf H, Bjerregard PM, Jerkeman M. The addition of etoposide to CHOP is associated with improved outcome in ALK+ adult anaplastic large cell lymphoma: A nordic lymphoma group study. Br J Haematol. 2017; 178: 739-746.
12. Pro B, Advani R, Brice. Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood. 2017; 130: 2709-2717.
13. Brentuximab Vedotin. Combination chemotherapy in treating patients with cd30-positive peripheral t-cell lymphoma. Retrieved from Clinical Trials. 2018.