Diagnostic Pathology

CASE REPORT Open Access

ALK+anaplastic large cell lymphoma involving the bladder: case report and review of the literature

Ying Zhao[1], Wenqiang Qiu[1], Xiangtao Weng[2], Chiming Gu[2*] and Siyi Li[2*]

Abstract

We reported a case of anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALK+ALCL) involving the bladder. The patient was a 27-year-old female, whose main clinical symptoms included fever, painless lymphadenopathy, and hematuria. Imaging studies suggested a bladder mass. The bladder mass was maximally resected through transurethral bladder tumor resection. The pathology report indicated a malignant tumor of the bladder. Based on immunohistochemical and gene rearrangement results, the diagnosis was confirmed as ALK+ALCL. After undergoing five cycles of treatment with the BV+CHP chemotherapy regimen, the patient's condition is currently stable, and no tumor recurrence was observed upon re-examination. ALK+ALCL involving the bladder is very rare, and early diagnosis is challenging. By reviewing the diagnostic and treatment process of this patient, and in conjunction with a review of modern literature on the disease's incidence characteristics, treatment protocols, and prognosis, this aims to provide a reference for clinicians in diagnosing and treating this condition, thereby reducing delays.

Keywords Bladder, Lymphoma, ALCL, ALK+ALCL

Introduction

Anaplastic large cell lymphoma (ALCL) is a rare group of malignant tumors derived from CD30+T-lymphocytes or NK cells and is classified as a type of non-Hodgkin lymphoma. The pathology reveals diffuse macrocytic proliferation characterized by heterogeneity and pleomorphism [1]. According to the World Health Organization Classification of Lymphomas, 5th edition, ALCL can be classified into four subtypes: anaplastic lymphoma kinase (ALK)-positive ALCL (ALK+ALCL), ALK-negative ALCL (ALK-ALCL), primary cutaneous ALCL (pcALCL), and breast implant-associated ALCL (BIA-ALCL) [2]. While bladder tumours are common, most are uroepithelial carcinomas, with bladder lymphomas being very rare. The main clinical manifestations of bladder lymphoma include macroscopic hematuria, dysuria, urinary frequency, nocturia, and abdominal or back pain [3]. Mucosa-associated lymphoid tissue lymphoma is by far the most common subtype of bladder lymphoma reported, followed by diffuse large B-cell lymphoma, while ALCL is rarely reported [4, 5]. A 27-year-old female patient with ALK+ALCL was admitted to the Department of Urology at Guangdong Provincial Hospital of Traditional Chinese Medicine, Ersha Island Hospital, in

*Correspondence:
Chiming Gu
guchiming@gzucm.edu.cn
Siyi Li
924289644@qq.com
[1]The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, China
[2]The Second Affiliated Hospital of Guangzhou University of Chinese Medicine (Guangdong Provincial Hospital of Traditional Chinese Medicine), Guangzhou, China

December 2023. Combined with modern literature, it is reported as follows.

Case report

Female patient, 27 years old. In August 2023, she began to present with enlarged left inguinal lymph nodes. On October 9, she was hospitalized in an outside hospital with recurrent fever (maximum temperature 40 °C) after exertion. On admission, she had bilateral cervical lymph nodes and bilateral inguinal lymph node enlargement. The bone marrow smear suggests trilineage hyperplasia with an elevated red lineage ratio, slightly delayed maturation of megakaryocytes, and a few hemophils. Whole-body positron emission computed tomography (PET/CT) revealed no signs of hypermetabolic malignancy in the parenchymal organs. However, it did show multiple enlarged lymph nodes throughout the body with moderately elevated metabolism, which was interpreted as reactive hyperplasia of the lymph nodes or giant lymph node hyperplasia.On 7 December 2023, the patient started to develop hematuria with bright red urine, accompanied by urinary frequency and urgency, urinary pain, and multiple enlarged lymph nodes all over the body. Enhanced CT scan of the abdomen and pelvis showed bladder occupancy and multiple lymph node enlargement in abdominal, pelvic, retroperitoneal, and bilateral inguinal regions, which was considered malignant and possibly lymphoma. On 12 December 2023, she was admitted to the Department of Urology, Ersha Island Hospital, Guangdong Provincial Hospital of Traditional Chinese Medicine. At the time of admission, the patient had a urinary catheter in place, and continuous bladder irrigation was performed. This procedure revealed significant hematuria, characterized by bright red urine without blood clots. The patient also experienced feelings of fullness and distension in the lower abdomen, along with palpable enlargement of superficial lymph nodes in the neck and groin on both sides. Enhanced CT scan of the abdomen and pelvis suggests the presence of a cystic solid soft tissue mass on the left side of the uterus and irregular thickening of the bladder wall, raising the possibility of malignant tumors of the ovary and bladder. Additionally, multiple enlarged lymph nodes are considered to be metastatic(Fig. 1). On December 12, 2023, the patient underwent transurethral resection of a bladder tumor (TURBT) and cystoscopy. Intraoperatively, a large dark red blood clot was

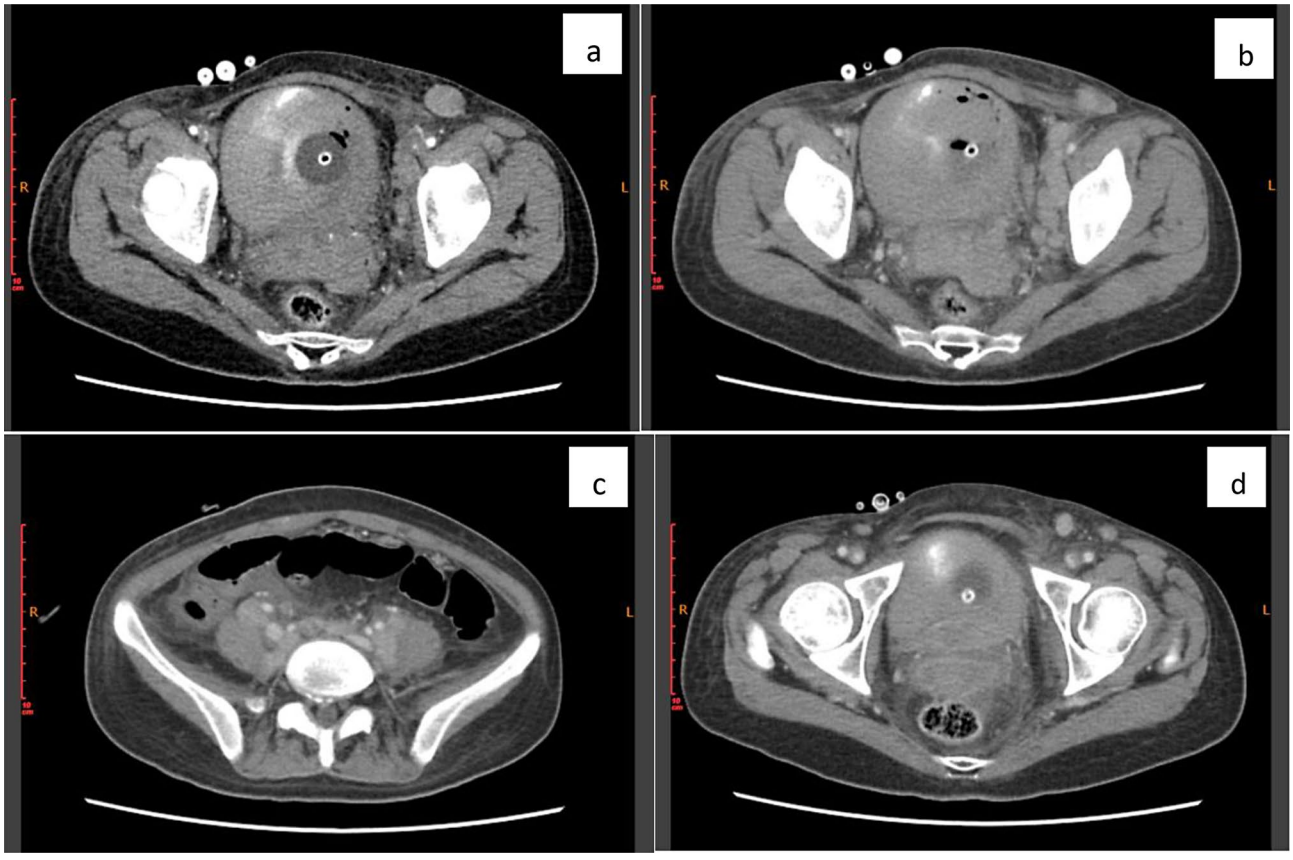

Fig. 1 Contrast-enhanced CT scan of the abdomen and pelvis: **a**.The bladder wall is unevenly thickened. Striated slightly hyperdense shadows are seen in the bladder with a CT value of approximately 61–77 HU. Intravesical catheterised bulb tube is left in place. **b**-**d**. Retroperitoneal, pelvic, and bilateral inguinal multiple enlarged lymph nodes, some of which are fused.

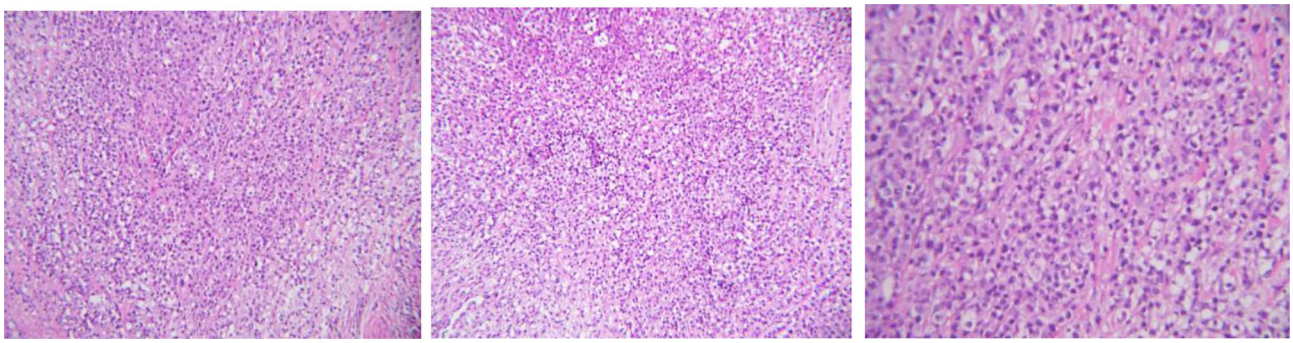

Fig. 2 H&E staining in the urinary bladder sample of ALK + ALCL

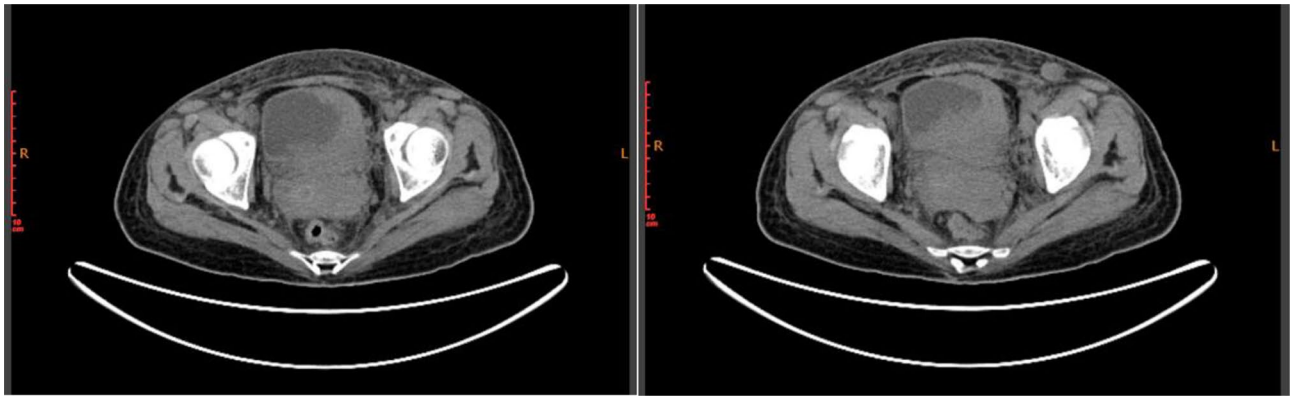

Fig. 3 2024-12-18 PETCT: The bladder is well filled. Diffuse inhomogeneous thickening of the bladder wall. SUVmax 22.09

observed in the bladder. A distinct neoplastic mass was visible from the bladder neck and bladder triangle to the left wall, measuring approximately 6 cm × 5 cm. The surface of the mass was inflamed and swollen, with evidence of mucosal inflammation and oozing blood. The ureteral orifices were not accessible bilaterally. The mass was maximally excised and sent for pathological testing (Fig. 2). Molecular pathology results: EBER (-); T-cell lymphoma clonal gene rearrangement test results were: TCRB: TCRBA (-), TCRBB (-), TCRBC(+); TCRD (+); TCRG: TCRGA (+), TCRGB (+). B-cell lymphoma clonal gene rearrangement test results: negative for IGH, IGK, and IGL gene rearrangements. Immunocytochemistry result: CD3 (partial +), CD5 (partial +), CD4 (-/+), CD20 (-), CD79a (-), CD19 (-), CD10 (-), Bcl-6 (-), MUM-1 (-), Ki67 (80% +), CD21 (-), Bcl-2 (-).CD23 (-),Cyclin D1 (-), CD30(+), ALK(+), CD15(-), P53(wild type), LCA(small amount of +), CD117(-), MPO(-), SALL4(-), OCT3/4(-), PLAP(-), AFP(-), GPC3(-), CD68, CD163(histiocyte+), CK(-). The results of the pathology report showed a malignant tumour of the bladder, which, in combination with immunohistochemistry and gene rearrangement results, was consistent with ALK + ALCL. The patient was transferred to the haematology department and a review of whole body PET/CT showed diffuse inhomogeneous thickening of the bladder wall. Multiple lymph nodes throughout the body were enlarged and metabolically increased, consistent with lymphomatous changes, and the lesions were significantly enlarged and increased compared to the whole-body PET/CT in the outside hospital (Fig. 3). Bone marrow aspiration results showed that the lymphoma did not involve the bone marrow. She was given BV + CHP (Vibutuximab + Cyclophosphamide + Doxorubicin + Dexamethasone) + Cedarbenazine chemotherapy regimen and has now completed 5 courses of treatment. In February 2024, a whole-body PET/CT scan suggested complete suppression of tumor activity consistent with lymphatic therapy, along with suspicious soft tissue thickening around the anastomosis of the posterior bladder wall following electrosurgery (Fig. 4). At present, the patient has no special discomfort for the time being except for mental fatigue and weakness.

Discussion

ALCL is a rare type of peripheral T-cell lymphoma (PTCL) that accounts for approximately 2% of non-Hodgkin's lymphomas in adults and 10–15% of non-Hodgkin's lymphomas in children and adolescents [6]. About 60% of ALCL patients are ALK+, which results from chromosomal abnormalities, most commonly due to the fusion of the ALK gene on chromosome 2 with the NPM gene on chromosome 5. In contrast, ALK- patients usually

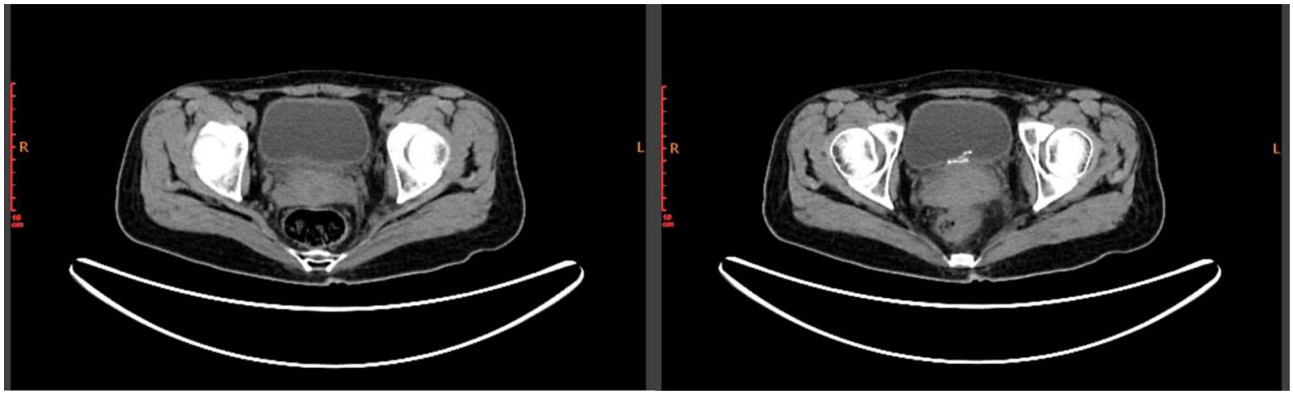

Fig. 4 2024-2-19 PETCT: The bladder is well filled. There appears to be a few soft tissue thickening shadows around the anastomosis in the posterior wall of the bladder. SUVmax 8.8

exhibit abnormalities on other chromosomes, such as TP63, DUSP22, TYK2, and ERBB4 [7]. ALK+ALCL typically occurs in male children and adolescents, whereas ALK- ALCL is more common in older individuals, with comparable incidence rates in both sexes [8]. The prognosis for ALK+ALCL is significantly better than that for ALK- ALCL, with a 5-year survival rate of up to 70% [9]. The clinical staging of ALCL is usually divided into four stages (I-IV), and most patients are already in stage III or IV at the time of diagnosis. The main clinical manifestations include persistent local or systemic lymph node enlargement, often accompanied by fever, malaise, weight loss, and other symptoms [10]. A study by Falini et al. showed that about 60% of ALK+ALCL cases involve extra-nodal organs, with the most common sites being the skin bone, soft tissues, bone marrow, lungs, and liver. Cases involving the bladder are very rare [11]. The majority of reported cases of ALK+ALCL involving the bladder have been in men, and common symptoms include hematuria, urinary frequency, urgency, and abdominal pain Patients with ALK+ALCL are generally younger compared to those with primary mucosa-associated lymphoid tissue (MALT) lymphoma or primary diffuse large B-cell lymphoma (DLBCL) of the bladder [5, 12–19].

Since ALK+ALCL involving the bladder is extremely rare, obtaining a definitive diagnosis is crucial. Pathological features play a key role in diagnosing ALK+ALCL. Characteristic cellular structures can be observed microscopically. The cells are medium to large-sized and exhibit irregular morphology. The nuclei are eccentric, and may be horseshoe- or renal-shaped, with distinct nucleoli visible. Additionally, the cytoplasm is rich in eosinophilic granules [20]. Additionally, the positive expression of CD30 in immunohistochemical staining is a key marker for ALCL. For the diagnosis of ALK+ALCL, several immunostains are supportive, including CD30, EMA, ALK, CD2, CD4, CD5, TIA1, granzyme B, perforin, CD45, CD45RO, CD61, CD25 (strong), and BNH9. In contrast, the diagnosis of ALK-ALCL is supported by different stains, such as CD15, CD20, CD79a, cytokeratins, Bcl-2, PAX5/BSAP, PGM1, and EBV (including EBER and LMP1) [10, 23]. Genetic tests, such as fluorescence in situ hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR), are also valuable in the diagnosis of ALK+ALCL. ALK+ALCL is characteristically manifested by rearrangements of the ALK gene. The ALK gene is located on chromosome 2 and is activated by chromosomal rearrangements [21], most commonly t(2;5)(q23;q35), which leads to ALK activation and accounts for approximately 80% of cases. Currently, ALK+ALCL can be diagnosed through immunohistochemistry (IHC) for ALK expression, fluorescence in situ hybridization (FISH) for detecting 2q23 breaks, and reverse transcription polymerase chain reaction (RT-PCR) for identifying the fusion of the NPM1 and ALK genes [22].

ALK+ALCL can be treated with radiotherapy, chemotherapy, and bone marrow transplantation. For newly diagnosed patients, anthracycline-based chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CHOEP (CHOP+etoposide), or dose-adjusted EPOCH (DA-EPOCH: etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone) are administered [23]. Although the above regimens can improve patients' 5-year progression-free survival (PFS) and overall survival (OS) to a certain extent, some patients still experience relapse [24]. For those with relapsed and refractory ALK+ALCL, platinum-based regimens such as DHAP (dexamethasone, cisplatin, high-dose cytarabine), ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and carboplatin), ICE (isocyclophosphamide, etoposide, and carboplatin), and GDP (gemcitabine, dexamethasone, and cisplatin) are often used [25, 26]. Stem cell transplantation, including autologous hematopoietic stem cell transplantation (auto-HCT) and allogeneic stem

cell transplantation (Allo-HCT), may be considered after the administration of ALK inhibitors [27] or high-dose chemotherapy [28, 29]. Brentuximab vedotin (BV) is a monoclonal antibody-drug conjugate that targets CD30-expressing lymphomas [30].The results of a Phase III randomized trial showed that the BV+CHP chemotherapy regimen was superior to the CHOP chemotherapy regimen for the treatment of previously untreated CD30+PTCL [31] and is now one of the first-line chemotherapy options for ALK+ALCL.

The prognosis for patients with ALK+ALCL is significantly better than that for other PTCL, with a relapse-free survival rate of about 60% and an overall remission rate of up to 90%. The International Prognostic Index (IPI) and Prognostic Index for T-cell Lymphoma (PIT) scores can be used to predict the prognosis of ALK+ALCL patients [20]. In general, factors such as age, gender, disease duration, clinical stage, and tumor load have a significant impact on prognosis. Younger patients, female patients, early diagnosis, and lower tumor load are usually associated with a better prognosis [32]. However, some patients experience relapse or drug resistance during treatment, which makes the prognosis uncertain. Therefore, close follow-up and individualized treatment strategies are essential to improve patient survival and quality of life.

A search in PubMed using the keywords "anaplastic large cell lymphoma" and "bladder" yielded a total of eight reported cases of ALK+ALCL involving the bladder. The most common clinical symptom reported was hematuria. The majority of these patients were male, aged 22 to 59 years [5, 12, 15, 16, 18, 19, 33, 34]. One HIV-positive male patient died 9 months after his diagnosis [16]. Two 59-year-old male patients, both presenting with unexplained fever as their first symptom and negative tests for infections and tumor-related conditions, were initially considered to have adult onset Still's Disease (AOSD). However, the patients rapidly progressed to macrophage activation (hemophagocytic) syndrome (MAS). The final diagnosis of ALK+ALCL was confirmed by cystoscopic pathology.Both patients died 39 days after the onset of the disease [19, 34]. The remaining patients were in complete remission after receiving chemotherapy with the CHOP regimen at the time of the publication of the relevant paper. In this case, the first symptom of the young female patient was enlarged lymph nodes, followed sequentially by unexplained fever and hematuria. The diagnosis of ALK+ALCL of the bladder was finally confirmed by genetic testing and immunohistochemistry. Unlike the previously reported cases, she received the BV+CHP chemotherapy regimen. She has currently completed five treatment cycles and has no specific discomfort aside from mental fatigue and weakness. The follow-up PET/CT scan indicates that the originally enlarged lymph nodes in multiple areas of the body have significantly shrunk and decreased compared to before. There are currently no noticeably enlarged lymph nodes, with no increased metabolic activity, and the tumor activity is completely suppressed. These cases illustrate that for ALK+ALCL involving the bladder, timely diagnosis and treatment can lead to a favorable prognosis.

Conclusion

The patient in this case was ultimately diagnosed with ALK+ALCL through bladder biopsy. After receiving BV+CHP chemotherapy, the condition was rapidly controlled, and the prognosis is favorable. The key is to be aware of the possibility of lymphoma involving the bladder. However, early diagnosis of ALK+ALCL affecting the bladder is challenging, so there is a need to seek better diagnostic methods. For example, it may be possible to explore changes in metabolites in the blood or urine of patients with ALK+ALCL to identify suitable biological markers for the early diagnosis of ALK+ALCL. Researchers still need to continue exploring.

Author contributions

Y.Z.and W.Q.: Writing - Original Draft; X.W.: Conceptualization; C.G.: Supervision; S.L.: Writing - Review & Editing. All authors read and approved the final manuscript.

Funding

This study was supported by Distinguished Talent Project at Guangdong Provincial Hospital of Traditional Chinese Medicine (No. BJ2022YL04) and Guangzhou Science and Technology Bureau (No. 202201020350) and Special Project of Guangdong Provincial Hospital of Traditional Chinese Medicine (No. YN2023WSSQ03).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Guangdong Provincial Hospital of Traditional Chinese Medicine. Written informed consent was obtained from the participants for publication of the details of their medical case and any accompanying images.

Consent for publication

Informed consent has been obtained from the patient included in this study.

Competing interests

The authors declare no competing interests.

Received: 30 June 2024 / Accepted: 3 December 2024
Published online: 18 December 2024

References

1. Falini B, Pileri S, Pizzolo G, et al. CD30 (Ki-1) molecule: a new cytokine receptor of the tumor necrosis factor receptor superfamily as a tool for diagnosis and immunotherapy. Blood. 1995;85(1):1–14.
2. Alaggio R, Amador, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: lymphoid neoplasms. Leukemia. 2022;36(7):1720–48.
3. Venyo AK. Lymphoma of the urinary bladder. Adv Urol. 2014;2014:327917.

4. Kempton CL, Kurtin PJ, Inwards DJ, Wollan P, Bostwick DG. Malignant lymphoma of the bladder: evidence from 36 cases that low-grade lymphoma of the MALT-type is the most common primary bladder lymphoma. Am J Surg Pathol. 1997;21(11):1324–33.
5. Liang X, Wang Y, Zhang J, et al. Anaplastic lymphoma kinase-positive anaplastic large-cell lymphoma with involvement of the urinary bladder: a case report and review of literature. Onco Targets Ther. 2015;8:1143–7.
6. Kinney MC, Higgins RA, Medina EA. Anaplastic large cell lymphoma: twenty-five years of discovery. Arch Pathol Lab Med. 2011;135(1):19–43.
7. Wu R, Lim MS. Updates in pathobiological aspects of anaplastic large cell lymphoma. Front Oncol. 2023;13:1241532.
8. Stein H, Foss HD, Dürkop H, et al. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood. 2000;96(12):3681–95.
9. Guru Murthy GS, Hamadani M, Bhatt VR, et al. Systemic anaplastic lymphoma kinase-positive anaplastic large cell lymphoma: a Population-based analysis of incidence and survival. Clin Lymphoma Myeloma Leuk. 2017;17(4):201–6.
10. Kaseb H, Mukkamalla SKR, Rajasurya V. Anaplastic large cell lymphoma. StatPearls. Treasure Island (FL). Volume 3. StatPearls Publishing; 2023.
11. Falini B, Pileri S, Zinzani PL, et al. ALK + lymphoma: clinico-pathological findings and outcome. Blood. 1999;93(8):2697–706.
12. Pai SA, Naresh KN, Patil PU. Systemic anaplastic large cell lymphoma presenting as a bladder neoplasm. Leuk Lymphoma. 2004;45(4):841–3.
13. Allory Y, Merabet Z, Copie-Bergman C, Lange F, Yiou R, Gaulard P. Sarcomatoid variant of anaplastic large cell lymphoma mimics ALK-1-positive inflammatory myofibroblastic tumor in bladder. Am J Surg Pathol. 2005;29(6):838–9.
14. Hughes M, Morrison A, Jackson R. Primary bladder lymphoma: management and outcome of 12 patients with a review of the literature. Leuk Lymphoma. 2005;46(6):873–7.
15. Murphy AJ, O'Neill P, O'Brien F, et al. Anaplastic large cell lymphoma: a unique presentation with urinary bladder involvement: a case report. Int J Surg Pathol. 2005;13(4):369–73.
16. Proca DM, De Renne L, Marsh WL Jr, Keyhani-Rofagha S. Anaplastic large cell lymphoma in a human immunodeficiency virus-positive patient with cytologic findings in bladder wash: a case report. Acta Cytol. 2008;52(1):83–6.
17. Blick C, Abdelhadi S, Bailey D, Muneer A, Anaplastic. T-cell, Non-hodgkin's lymphoma presenting with haematuria. Sci World J. 2008;8:342–5.
18. Gómez-Román JJ, Cobo ML, Val-Bernal JF. Anaplastic lymphoma kinase-positive anaplastic large cell lymphoma presenting as a bladder neoplasm. Pathol Int. 2008;58(4):249–52.
19. Chen H, Li Y, Nand S, Quek ML, Kini AR, Barkan GA. Anaplastic large cell lymphoma involving the urinary bladder: a case report and review of the literature. Diagn Cytopathol. 2015;43(1):60–5.
20. Ferreri AJ, Govi S, Pileri SA, Savage KJ. Anaplastic large cell lymphoma, ALK-positive. Crit Rev Oncol Hematol. 2012;83(2):293–302.
21. Cao Z, Gao Q, Fu M, Ni N, Pei Y, Ou WB. Anaplastic lymphoma kinase fusions: roles in cancer and therapeutic perspectives. Oncol Lett. 2019;17(2):2020–30.
22. Kalinova M, Mrhalova M, Kabickova E, et al. Molecular screening in anaplastic lymphoma kinase-positive anaplastic large cell lymphoma: Anaplastic Lymphoma Kinase Analysis, next-generation sequencing Fusion Gene Detection, and T-Cell receptor immunoprofiling. *Mod Pathol*. Published Online January. 2024;23. 10.1016.
23. Sibon D, Nguyen DP, Schmitz N, et al. ALK-positive anaplastic large-cell lymphoma in adults: an individual patient data pooled analysis of 263 patients. Haematologica. 2019;104(12):e562–5.
24. Zhang XR, Chien PN, Nam SY, Heo CY. Anaplastic Large Cell Lymphoma: Mol Pathogenesis Treat Cancers (Basel). 2022;14(7):1650.
25. Ellin F, Landström J, Jerkeman M, Relander T. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. Blood. 2014;124(10):1570–7.
26. Yao YY, Tang Y, Zhu Q, et al. Gemcitabine, oxaliplatin and dexamethasone as salvage treatment for elderly patients with refractory and relapsed peripheral T-cell lymphoma. Leuk Lymphoma. 2013;54(6):1194–200.
27. Prokoph N, Larose H, Lim MS, Burke GAA, Turner SD. Treatment options for paediatric anaplastic large cell lymphoma (ALCL): current standard and beyond. Cancers (Basel). 2018;10(4):99.
28. Furqan F, Ahn KW, Chen Y, et al. Allogeneic haematopoietic cell transplant in patients with relapsed/refractory anaplastic large cell lymphoma. Br J Haematol. 2023;200(1):54–63.
29. Du J, Yu D, Han X, Zhu L, Huang Z. Comparison of allogeneic stem cell transplant and autologous stem cell transplant in refractory or relapsed peripheral T-Cell lymphoma: a systematic review and Meta-analysis. JAMA Netw Open. 2021;4(5):e219807.
30. Katz J, Janik JE, Younes A. Brentuximab Vedotin (SGN-35). Clin Cancer Res. 2011;17(20):6428–36.
31. Horwitz S, O'Connor OA, Pro B, et al. Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): a global, double-blind, randomised, phase 3 trial. Lancet. 2019;393(10168):229–40.
32. Guru Murthy GS, Hamadani M, Bhatt VR, Dhakal I, Mehta P. Systemic anaplastic lymphoma kinase-positive anaplastic large cell lymphoma: a Population-based analysis of incidence and survival. Clin Lymphoma Myeloma Leuk. 2017;17(4):201–6.
33. Yamazaki R, Koda Y, Abe R, et al. Rinsho Ketsueki. 2021;62(1):25–9.
34. Lawrenz J, Tomal J, Towne J, Johnson B, Rieger B. 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(2):95–101.

Publisher's note