Case Report

ANNALS OF MEDICINE & SURGERY

OPEN

Primary bladder B-cell lymphoma: a rare case report and review of literature

Jerry Lorren Dominic, MD[a], Rohit Ganduboina, MBBS[d], Palak Dutta, MD[e,*], Khalid Gubran, MD[b], Michael Lord Toussaint, MD[f], Derek Michael Isrow, MD[c]

Introduction and importance: Primary bladder lymphoma accounts for a mere fraction of vesical tumours and extranodal lymphomas, which mostly affect women. IGH-BCL2 translocation, which occurs in 80–100% of Western follicular variants but only 60% in Asian communities, must be studied to determine its effects on prognosis and treatment. This study analyses and compares relevant literature and data for the authors' case report.

Case presentation: The authors report a 69-year-old Caucasian female with one gross haematuria episode and no smoking history. Computed tomography (CT) showed a bilateral massive intraluminal mass left ureterovesical junction, hydronephrosis, and hydroureter.

Clinical discussion: Following the removal of a massive transurethral urinary bladder tumour, histological examination revealed lymphoma cells positive for IRTA and LMO2 but negative for IGH-BCL2. After these analyses, the patient received 3 weeks of 30 Gy/15 f IMRT/IGRT. Comparisons were made to previous case reports' histopathology.

Conclusion: The current case report emphasizes the rarity of primary bladder lymphoma and the absence of the IGH-BCL2 fusion gene. Following the successful administration of 30 Gy of radiation therapy, the patient's prognosis improved. The report emphasizes clinical vigilance and timely management while also urging further investigation.

Keywords case report: left hydronephrosis, lymphoma bladder, radiotherapy post-surgery

Introduction

Isaacson and Wright first proposed mucosa-associated lymphoid tissue (MALT) lymphomas in 1983; these are low-grade B-cell lymphomas that replicate MALT's characteristics and account for the majority of B-cell lymphomas occurring in the gastrointestinal tract, lung, salivary glands, and urinary bladder[1,2]. Primary malignant lymphoma of the bladder is a rare variant that impacts females. While secondary bladder involvement is more common in advanced lymphomas, primary bladder lymphoma is

HIGHLIGHTS

- Rare occurrence: Primary lymphoma of the bladder is an extremely rare malignancy, constituting less than 1% of vesical tumours and less than 0.02% of extranodal lymphomas, with a unique prevalence pattern in different populations.
- Immunohistological variance: The case report highlights significant immunohistological variance in comparison to Western cases, with the absence of IGH-BCL2 fusion in about 60% of cases in Asian communities, diverging from the prevalent 80–100% in Western variants.
- Case presentation: The case involves a 70-year-old Caucasian female with a singular episode of gross haematuria. The clinical journey, from diagnosis through radiotherapy, is detailed, providing insights into the challenges and outcomes associated with the management of primary lymphoma of the bladder.
- Treatment modalities: The patient underwent transurethral urinary bladder tumour resection followed by radiotherapy-based treatment. The chosen treatment strategy, dosage, and duration are discussed, contributing valuable information to the existing knowledge on therapeutic interventions for this rare condition.
- Immunohistochemical patterns: The case report presents unique immunohistochemical patterns, including positivity for IRTA1 and LMO2, along with the absence of IGH-BCL2 fusion. This distinctive profile contributes to the expanding understanding of the varied molecular characteristics of primary lymphoma of the bladder.

[a]Department of General Surgery, University of Miami Miller School of Medicine/Jackson Memorial Hospital, Departments of [b]General Surgery, [c]Radiation Oncology, University of Miami/Jackson Memorial Hospital & Sylvester Cancer Center, Miami, FL, [d]NRI Institute of Medical Sciences, Vishakhapatnam, India, [e]Kyiv Medical University, Kyiv, Ukraine and [f]St. George's University School of Medicine, West Indies, Grenada

Jerry Lorren Dominica and Rohit Ganduboina contributed equally to the paper and they both are co First authors

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Medical Student, Kyiv Medical University, Kyiv, Ukraine. Tel.: +91 959 991 4064. E-mail: duttapalak05@gmail.com (P. Dutta).

Annals of Medicine & Surgery (2024) 86:3652–3657

Received 9 February 2024; Accepted 28 March 2024

Published online 24 April 2024

http://dx.doi.org/10.1097/MS9.0000000000002051

a very uncommon cancer that only makes up about 1% of bladder tumours and less than 0.02% of lymphomas that are not in lymph nodes[3–5].

The bladder and the hindgut share a developmental relationship, with a hypothesis stating lymphoid tissue produced from the embryonic cloaca may be the origin of bladder lymphomas. However, it is more likely that, like other MALT lymphomas, acquired lymphoid follicles, such as those seen in follicular cystitis brought on by persistent irritation of the bladder by inflammation, are the source. Additionally, it also developed in bladders that were healthy and free of cystitis[6,7]. The patient usually presents in the sixth to seventh decade with haematuria along with dysuria, frequency, and nocturia[8,9]. The IGH-BCL2 translocation (14:18) (q32: q21) is present in 80–100% of follicular variants in Western countries, whereas in Southeast Asia, including Japan, the incidence of translocation is lower—about 60%[10].

When a case of bladder lymphoma is suspected, the diagnosis is by exclusion after a negative assessment of disease extension, which includes a bone marrow biopsy, computed tomography (CT), and positron emission tomography (PET) to look for additional nodal or extranodal involvement. Primary lymphoma of the bladder is diagnosed by exclusion made on biopsy with immunohistochemical study[11]. The treatment modalities include chemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), surgical excision, and radiotherapy[12]. We report a case of a 69-year-old female with unique bladder lymphoma treated with radiotherapy.

This case report has been reported in line with the SCARE Criteria[13]

Patient information

A Caucasian 69-year-old G_2P_2 female presented to gynaecology with a single episode of gross haematuria. She was referred to a urologist in November 2021; the patient denied any history of weight loss, back or bone pain, or complaints of increased frequency and urgency in urination. Nonsmoker, no history of renal stones, and past and family history were not significant.

Clinical findings

An examination showed an obese female; a manual pelvic exam revealed a mobile mass and no abnormalities on the systemic exam. CT workup revealed a bilateral large intraluminal mass of 5.7 cm on the left and 2.8 cm on the right, as depicted in Figure 1, consistent with malignancy associated with obstruction of the left ureterovesical junction and associated hydronephrosis and hydroureter without significant decline in kidney function.

Diagnostic assessment

Immunohistochemistry

Pathology from cystoscopy with TURBT showed a low-grade B-cell marginal lymphoma, cytology was negative for high-grade urothelial carcinoma, and urine analysis revealed large blood and leucocytes. Immunohistochemical studies showed lymphoma was positive for CD20 and BCL2 while negative for CD5. Lymphoma cells appeared kappa light chain restricted, as detected by kappa and lambda ultrasensitive RNA in situ hybridization (RNA ISH).

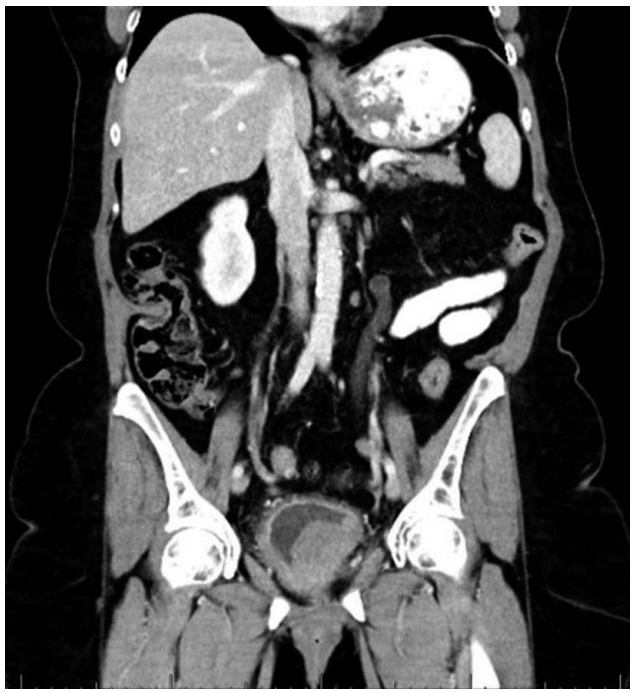

Figure 1. Computed tomography scan showing bladder intraluminal mass.

The B cells in the follicles were positive for BCL6, CD10, and HGAL. The BCL6 immunostaining showed patchy staining within the nodular aggregates and irregularities in the nodular borders. There were clusters of BCL6-negative cells within the BCL6-positive aggregates, which suggested follicular colonization. The overall findings pointed towards CD5-negative low-grade B-cell lymphoma, a small cell type. The unusual histologic features made the classification difficult. A differential diagnosis

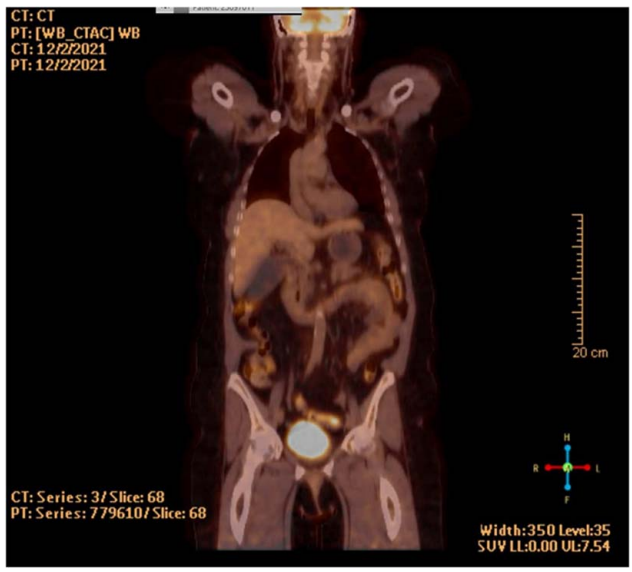

Figure 2. Positron emission tomography-computed tomography showing asymmetric thickening of the bladder wall.

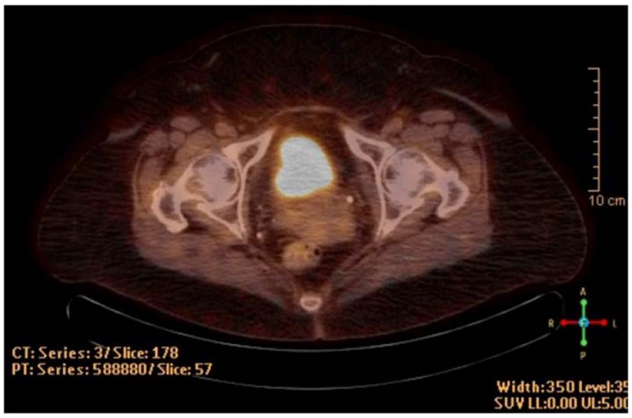

Figure 3. Positron emission tomography-computed tomography post therapy showing no abnormal activity within the bladder wall.

of marginal zone lymphoma with prominent follicular colonization with marginal zone lymphoma cells and follicular lymphoma negative for CD10 and BCL2 was made. Later, it was classified as marginal zone lymphoma due to the demonstration of colonization, the high proliferative rate among BCL6-positive cells, and the lack of CD10 and BCL2 expression among lymphocytes of the non-germinal centre. However, FISH studies revealed the absence of the t (14;18) translocation. Further studies identified that a subset of lymphoma cells was positive for IRTA1. LMO2 was positive in most lymphoma cells. IGH-BCL2 fusion was not detected. Overall findings were consistent with marginal zone lymphoma with extensive colonization of reactive follicles.

Radiology

PET-CT showed asymmetrical thickening of the left posterolateral bladder wall, causing obstruction of the left ureterovesical junction, and associated with moderate hydroureteronephrosis of the left kidney, as shown in Figure 2. This extended to the right ureterovesical junction, causing mild hydroureteronephrosis of the right kidney. There was a focal increase in FDG uptake along the bladder wall measuring up to 3 cm; the SUV was 28.5 cm greater than the background. Hologic urine activity within the bladder. Adjacent soft-tissue stranding was identified. No suspicious FDG intake; avid abdominal or pelvic lymphadenopathy.

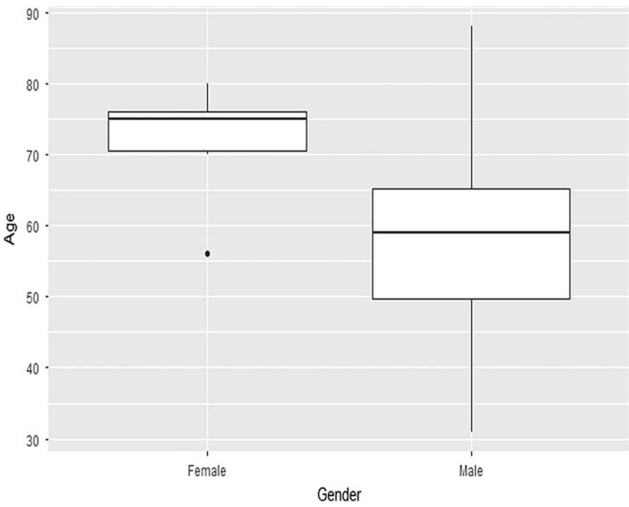

Figure 4. Boxplot representing cases of primary diffuse large B-cell lymphoma.

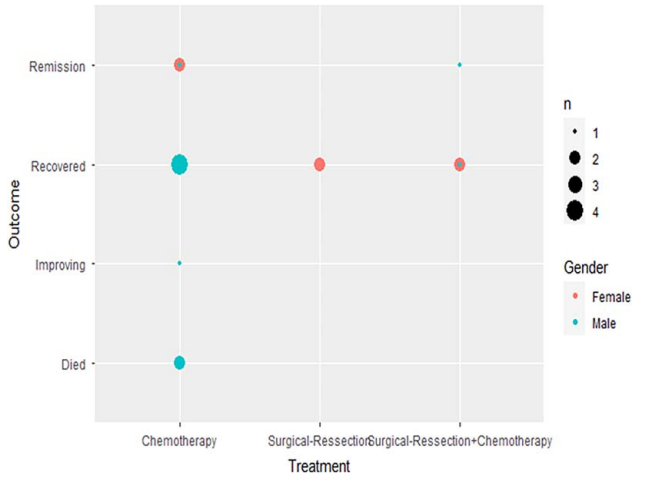

Figure 5. Graphical representation of therapeutic outcomes among cases of primary diffuse large B-cell lymphoma.

Diagnosis

The diagnosis of IAE MALT lymphoma of the bladder is made. The patient was referred to radiation oncology after discussing treatment options and outcomes.

Therapeutic intervention

Surgical intervention

After the diagnosis of malignant bladder cancer, the patient was posted for transurethral urinary bladder tumour resection (TURBT). The procedure was performed under general anaesthesia. During the procedure, a sessile tumour greater than 5 cm extending from the left bladder wall to the right posterior wall, without any papillary features, was observed. No distinction between the normal bladder wall and the tumour was identified; a large resection was performed using a recto scope, and samples obtained were sent for histopathological examination. Visualization of the left urethral orifice could not be achieved during the procedure. Urine was sent for cytology, and following the procedure, a Foley catheter was placed for monitoring. The patient was discharged with no issues and later referred to medical oncology.

Radiation therapy

After discussing the diagnosis and explaining the details of the treatment process and side effects, the patient was started on radiotherapy for the primary tumour. The patient was posted for 30 Gy/15 f with IMRT/IGRT to spare normal local tissues, including the bowel, rectum, and femoral heads. Radiotherapy was administered for 3 weeks in December 2021–February 2022. The patient tolerated the treatment without any adverse effects.

TABLE 1

Data from literature of primary DLBCL cases.

S. No	Author	Title	Year	Age[a]	Sex[a]	Severity	Markers	Treatment	Outcome
1	Xu *et al.*	Concurrent lung adenocarcinoma and bladder diffuse large B-cell lymphoma: a case report and literature review	2022	77	Female	NA	CD3, CD5, CD10, CD68-Negative, CD20, BCL2, BCL6- Positive	R2	Remission
2	Lokeshwar *et al.*	Diffuse large B-cell lymphoma presenting as LUTS: Clinical practice points	2022	57	Male	High	NA	Partial resection + Multi-Regimen therapy	Remission
3	Muta *et al.*	Diffuse Large B-cell Lymphoma Arising Primarily at the Stoma After Bladder Reconstruction Using Ileal Conduit	2012	76	Male	NA	CD10, BCL2-Negative, CD20, BCL6-Positive	R-THP-COP	Remission
4	Luketich *et al.*	EBV-positive diffuse large B-cell lymphoma presenting as symptomatic masses in the bladder trigone and unilateral kidney	2023	66	Male	High	CD20, BCL2, BCL6- Positive	R-CHOP	Improving
5	Sain *et al.*	Epstein–Barr virus-positive primary diffuse large B-cell lymphoma of the urinary bladder: a case report	2023	80	Woman	NA	CD10, CD20, BCL2, BCL6- Positive	Surgical-Ressection	Recovered
6	Hayashi *et al.*	Primary Diffuse Large B-Cell Lymphoma of the Bladder	2009	75	Woman	High	CD3- Negative, CD20- Positive	R-CHOP	Remission
7	Simpson *et al.*	Primary bladder lymphoma, diffuse large B-cell type: Case report and literature review of 26 cases	2015	48	Male	NA	BCL2, BCL6-Negative, CD10- Positive	R-CHOP	Recovered
8	Lee *et al.*	Diffuse Large B-Cell Lymphoma Arising within Ileal Neobladder: An Expanding Spectrum of Diffuse Large B-Cell Lymphoma Associated with Chronic Inflammation	2019	88	Male	NA	CD10, BCL6-Negative, CD20- Positive	R-CHOP	Recovered
9	Khurana *et al.*	Primary diffuse large B-cell lymphoma of the urinary bladder mimicking a clear cell variant of an infiltrating urothelial carcinoma	2010	75	Female	NA	CD3-Negative, CD10, CD20-Positive	Surgical-Resection	Recovered
10	Khaitan *et al.*	Primary Non-Hodgkin's Lymphoma of Urinary Bladder	2004	55	Male	NA	NA	CHOP	Died
11	Bhutani *et al.*	Primary extra nodal Non-Hodgkin's lymphoma of urinary bladder presenting as a bladder tumor: A case report	2020	40	Male	NA	CD5, CD10, BCL2-Negative, CD20-Positive	R-CHOP	Recovered
12	Hughes *et al.*	Primary bladder lymphoma: management and outcome of 12 patients with a review of the literature	2005	71	Female	NA	NA	CHOP	Recovered
13	Hughes *et al.*	Primary bladder lymphoma: management and outcome of 12 patients with a review of the literature	2005	31	Male	NA	NA	Doxycycline	Recovered
14	Hughes *et al.*	Primary bladder lymphoma: management and outcome of 12 patients with a review of the literature	2005	70	Female	NA	NA	Surgical-resection + CHOP	Recovered
15	Huang *et al.*	Simultaneous triple primary malignancies, including bladder cancer, lymphoma, and lung cancer, in an elderly male: A case report	2022	61	Male	NA	CD3, CD5, CD10-Negative, CD20, BCL2, BCL6-Positive	Surgical Resection + R-CHOP	Recovered
16	Kuhara *et al.*	A case of primary malignant lymphoma of the bladder	1990	56	Female	NA	NA	Surgical-Resection + Chemotherapy	Recovered
17	Gohji *et al.*	A case of primary malignant lymphoma of the urinary bladder	1985	63	Male	NA	NA	Chemotherapy	Died

Frequency of male:female- 0.59:0.41 ($n=$ 10 males, 7 females).

DLBCL, diffuse large B-cell lymphoma; NA, not applicable.

[a]Mean Age- 64.06 ± 15.00, Median Age- 66, Range- 57

Follow-up and outcome

Recovery was uneventful following radiotherapy; the patient had no complaints of altered urinary frequency or altered appetite. The cystoscopy performed did not reveal any residual tumours, but there was some tissue seen within the left urethral orifice. The renal scan performed post-radiotherapy revealed a normal right kidney and a small left kidney with no features of hydronephrosis. PET-CT performed in April 2022, as represented by Figure 3, showed no abnormal activity within the bladder wall; however, evaluation was limited due to underdistention and the presence of physiologic FDG activity within the urine. The prominence of the right pelvic calyceal system with hydroureter is observed, and no other suspicious FDG-avid supradiaphragmatic or infra-diaphragmatic lymphadenopathy is observed.

Discussion

Primary lymphoma of the bladder refers to the exceedingly rare development of lymphoid-based cellular proliferation that originates within urothelial tissues. Primary DLBCL of the bladder is a rare occurrence, with only a few published cases in the literature summarized in Table 1. Bladder lymphoma encompasses two primary pathological types, namely low-grade mucosa-associated lymphoid tissue, and high-grade diffuse large B-cell lymphoma (DLBCL). Conversely, anaplastic large cell lymphoma (ALCL) is an infrequent occurrence. Most primary bladder MALT lymphomas exhibit a gradual onset, a prolonged progression, and lack typical clinical symptoms. The most typical clinical symptom is gross haematuria, followed by frequent urination, urgency, and dysuria[14]. From an epidemiological perspective, it has been observed that primary lymphoma of the bladder exhibits a notable prevalence among females and individuals of Asian and European ancestry. However, the existing body of literature indicates a higher incidence among males, as illustrated in Figure 4[15,16].

Data from the literature shows positive outcomes among females in comparison to their counterparts, as depicted in Figure 5. The data gathered for the 2021 analysis by Lyapichev *et al*.[15] revealed a strong geographical predominance as well as a strong female predominance. Specifically, cases were clustered in Asia and Europe, with very few cases having been identified within the United States[15]. Patients are most often present with haematuria, dysuria, and abdominal or back pain[16].

A study of previously looked-at cases of primary MALT lymphoma of the bladder found that all of them had a CD20 B-lymphocyte marker that was positive. Significant variance is present in other associated markers, including but not limited to CD45, CD6, CD19, CD5, CD10, and BCL2[15,16]. No available cases have identified LMO2 positivity, as is presented in our report. Further investigation of available sources uncovered no other published reports of primary lymphoma of the bladder that exhibited similar immunohistochemical patterns as the current report.

Primary extranodal B-cell lymphomas are rare variations among bladder tumours, having a benign course[17]. Female preponderance exists, with a higher incidence among Asians. Extranodal variation of B-cell lymphomas has a good prognosis if occurring as a primary tumour among patients[5]. The current literature on these tumours is minimal, principally in immunohistochemistry, with less than one hundred reports.

Follicular B-cell lymphomas are associated with IGH-BCL2 fusion, which is lacking in the current case. This makes it unique among the literature currently available on these tumours. The absence of IGH-BCL2 fusion in the current case distinguishes it from other follicular B-cell lymphoma cases described in the current literature. LMO2 expression is the strongest predictor of a good prognosis, which could explain the positive outcome in the patient. Follicular lymphomas with IGH-BCL2 negativity have a favourable prognosis. The frequency of IGH-BCL2 fusion (90% of cases) exceeds that of LMO2 expression (50% of cases) in follicular lymphoma, suggesting that LMO2 expression is an imperfect surrogate for IGH-BCL2 fusion, which is the strongest predictor of good outcomes in patients with extranodal b-cell lymphoma. Retrospective analysis of the diffuse large B-cell lymphomas showed the presence of both MYC and IGH-BCL2 rearrangements for appropriate prognostic stratification. Thus, the presence of LMO2 and the absence of IGH-BCL2 can explain positive outcomes in the present patient[18–20].

Treatment of bladder cancer dates back a long time and includes surgical treatment, such as total cystectomy or partial cystectomy; however, it was found that there was no difference in the recurrence rate between surgical and non-invasive treatments. Since 1990, chemotherapy or radiation therapy has emerged as the primary treatment modality for bladder preservation[21]. Tu *et al*.[14] conducted a systematic review that suggested that TURBT should be prioritized as the initial treatment, followed by chemotherapy or radiotherapy either alone or in combination. A study conducted in 2003 showed that stage 1 B-cell lymphoma of the bladder responds well to radiotherapy and has a good survival rate at 30 Gy radiation[8]. Supporting literature is available in the form of an RCT concluding that reducing radiation to 30 GHz is beneficial in comparison to 45 GHz, which was indicated previously[22]. Also, as presented by a 2007 report showing that the chance of recurrence is inevitable, following radiation therapy with 45Gy-controlled radiation is necessary for better patient outcomes[23]. The current tumour has undergone 30 Gy radiation therapy. After 8 months of therapy, there are no indications of recurrence or localized areas of the tumour throughout the body. This signifies a favourable reaction to the therapy and implies a good prognosis for the patient. Regular monitoring is maintained to guarantee sustained progress and promptly identify any reoccurrence.

Conclusion

The literature on MALT lymphoma of the bladder is subtle; in addition, the complex immunohistochemistry makes its management a challenge for physicians. In the present report, we describe a rare example in a Caucasian female where the IGH-BCL2 fusion was not present, as evidenced by immunohistochemistry. The present tumour was treated successfully with 30 Gy radiation therapy without any complications. Inaccessibility of literature makes it difficult to explain the prognosis, but available literature points out the LMO2 presence and absence of IGH-BCL2 fusion on immunohistochemistry and radiation frequency used as the causes of excellent recovery by the patient.

The current case adds to the available literature that, though rare extranodal B-cell lymphoma (30% among all non-Hodgkin lymphomas) is infrequently glimpsed among Caucasians as an IGH BCL2-negative variant, bladder MALT lymphoma can

occur as a primary tumour, so clinical suspicion and prompt management should be done. Furthermore, the data regarding LMO2 positivity and IGH-BCL2 negativity in the setting of primary lymphoma of the bladder was not present in the available literature. Further research and reporting of similar cases are required to understand genetic associations in b-cell-derived lymphomas and immunohistological markers and determine the clinical and scientific significance of these findings.

Ethical approval

There is no requirement for ethical consent.

Consent

The patient's consent is obtained after he has been informed about the study. The patient well tolerated the therapy; there were no complaints of adverse reactions to radiation or recurrence.

Source of funding

No funding sources to disclose.

Author contributions

Conceptualization: J.L.D., R.G., P.D. Methodology: J.L.D., R.G., P.D. Validation: K.G., M.T., D.M.I. Formal analysis and investigation: J.L.D., R.G. Data curation: R.G., P.D. Writing—original draft: J.L.D., R.G., P.D., K.G., M.T., D.M.I. Visualization: J.L.D., R.G. Writing—review and editing: P.D., R.G. Editing: R.G. Supervision and project administration: J.L.D.

Conflicts of interest disclosure

There are no funding sources or conflicts of interest to disclose.

Research registration unique identifying number (UIN)

Research registration not aquired.

Guarantor

Dr Jerry Lorren Dominic is the principal investigator and guarantor for the paper.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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