

Original Article

Non-Hodgkin's primary lymphoma involving the genitourinary tract: histopathological experience from two tertiary hospitals, Western region, Saudi Arabia

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Abstract: Background: Urinary tract and male genital organ lymphoid neoplasms are uncommon, accounting for less than 5% of all primary extranodal lymphomas. There have only been a few small case series and isolated case reports describing the primary sites and subtypes of these neoplasms. The aim of the study is to investigate the pathological characteristics of patients diagnosed with primary Genitourinary (GU) lymphoma in at two major hospitals. Material and methods: We obtained cases that were diagnosed with primary GU lymphomas between 2005 and 2020. Pathology and immunohistochemistry slides were retrieved and reviewed, additional immunohistochemical markers were done on selected cases. Result: Herein we present a study of 11 patients. The mean age at diagnosis time was 46 years (range 24-71 years). Among urinary bladder, and ureter lymphomas, a slight female predominance was noted (3:2). Pathologic lymphoma subtype observed in our study were diffuse large B-cell lymphoma (DLBCL) (36%); mucosa-associated lymphoid tissue (MALT) lymphoma (18%); acute lymphoblastic lymphoma (B-LBL) (9%); high-grade B-cell lymphomas (27%) one of them with histomorphology of Burkitt-like large cell type, and a case of high-grade lymphoma, unclassifiable (9%). At the initial time of presentation, patients were commonly presented with non-specific signs and symptoms. Conclusion: Even though this study reaffirms the prevalence of DLBCL in GU system, it also sheds light on the variable range of lymphomas that can arise in these sites. The variety of subtypes highlights the significance of thoroughly characterizing lymphoma classifications through ancillary studies such as immunohistochemistry and other molecular/cytogenetic tests if needed, as they are crucial for achieving an accurate pathology diagnosis.

Keywords: Genitourinary, lymphoma, primary urinary tract lymphoma

Introduction

Lymphoma affecting the Genitourinary (GU) tract is not common and accounts for less than 5% of all primary extra nodal lymphoma cases. Early diagnosis of these lesions is crucial, as any delay in detecting them could result in their dissemination or transformation into high-grade lymphomas. A limited number of case series and case reports have been published regarding the primary lymphoma of the GU tract [1]. In of meantime, the two largest American series were released in the years 2009 and 2021 respectively [2, 3]. The objective of this study is to describe the nature of lymphoma that affects the urinary bladder, ureter, urethra, prostate, testis, and spermatic cord. We present a retrospective reviewed clinical data and

histologic findings of primary urinary tract lymphoma (PUTL) at two tertiary hospital institutions in the western region of Saudi Arabia. Lower urinary tract symptoms caused by lymphoma affecting the lower urinary tract, often lead to misdiagnosis as either urinary bladder cancer or prostate cancer. It is important to consider primary lymphoma as a possible diagnosis and maintain a high index of suspicion toward this differential. It is important to be particularly cautious when encountering any unusual lymphoid infiltration in the urinary bladder and prostate surgical specimens. Conversely, secondary GU involvement is a relatively common occurrence, especially in cases of widespread lymphoma. Clinical and radiological correlation is required along with histopathology conformation. When patients exhibit anoma-

lous findings in their physical examination, cystoscopy, or computed tomography (CT) scan, in the absence of systemic involvement, it is important to keep primary lymphoma in mind as a potential differential diagnosis. The available data on the clinicopathological pattern of PUTL in Saudi patients is limited to a few case reports, leaving a gap in the perception of the disease. More clinicopathological detail is required for better disease understanding. Therefore, the objective of this study was to investigate and describe the histopathological characteristics of PUTL cases diagnosed at two tertiary cancer institutions.

Materials and methods

The research was conducted at two tertiary cancer hospital facilities in the Western region, Saudi Arabia, King Abdulaziz University Hospital (KAUH) and King Faisal Specialist Hospital and Research Centre (KFSHRC). We retrieved cases from electronic archives of pathology reports spanning from 2005 to 2020, which showed a total of 11 occurrences of lymphoid neoplasms in various organs, including the urinary bladder, ureters, testes, spermatic cord, and prostate. The study included mass-forming lymphoproliferative tumors in GU tract areas such as lymphoblastic lymphoma/leukemia. Inclusion criteria were restricted to lymphomas arise primarily in the GU with proved histopathology diagnosis. Secondary GU involvement was excluded from the study. Data collected including patient information such as age at diagnosis, sex, clinical history, histology subtype, and outcome were documented.

We retrieved and examined slides that were stained with hematoxylin and eosin (H&E), and immunohistochemical (IHC) stains using an automated immunostainer (Leica Biosystems). Selected cases underwent additional immunohistochemical markers. The basic set of IHC tests carried out comprises cluster of differentiation (CD) 45/Leukocyte common antigen (LCA), CD20, Paired box-5 protein (PAX-5) (Leica Biosystems), CD7a, CD3, CD5, CD10, CD21, CD23, CD30, Cyclin-D1, BCL-2, BCL-6, multiple myeloma oncogene-1 (MUM-1), CD138, kappa, and lambda light chains, and Ki-67 proliferative index. In certain situations, supplementary IHC such as Activin A receptor like type 1 (ALK-1), Human Herpesvirus-8 (HHV-8), Terminal Deoxynucleotidyl Transferase (TdT), CD43, CD38,

CD138, and CD68 were conducted to provide a more precise characterization of the tumor's immunophenotype. By analyzing the tumor cytomorphology and immune profile, we reclassify old previous cases into updated diagnostic categories currently accepted world health organization (WHO) classification of hematolymphoid tumors 2022. The study archival material that had undergone fixation through 10% neutral buffered formalin (NBF), was also subsequently preserved in formalin-fixed paraffin-embedded (FFPE) form. Tumor blocks were sectioned at a thickness of 4 μm . (Leica Microsystems Plus Slides), positive-charged slides were used to mount the tissue sections, which were subsequently deparaffinized in xylene and rehydrated using an automated immunostainer (BenchMark XT, Ventana® Medical Systems Inc., Tucson, AZ, USA). The slides contained testable controls that were functional. Using the Ultra View or Optiview Universal DAB Detection Kit, tissue samples were subjected to deparaffinization and heat-induced antigen retrieval. Subsequently, the samples were incubated for a predetermined optimal duration with the specific antibody of interest. Following incubation, a hematoxylin II counterstain was used for 12 minutes, after which a blue coloring reagent was applied for 8 minutes, according to the manufacturer's directions (Ventana). All cases were analyzed microscopically at both low and high magnifications and classified according to the most recent WHO edition. The Ki-67 proliferative index was assessed manually, with percentage estimates based on the areas of the tumor showing the highest positive staining (**Table 1**). Approval for the study was granted (Reference No. 34-22)/(IRB-2024-CR-30).

Results

Our study identified eleven cases of primary lymphoma that were diagnosed through biopsy and resection which was confirmed clinically and pathologically to involve urinary tract and male genital organs. The average age at diagnosis was 46 years, with the age range varying from 24 to 71 years. Lymphomas affecting the urinary bladder and ureter show a slight female predominance (3:2) ratio. Exhibited symptoms were different based on tumor location, which included palpable mass (four patients), hematuria (three patients), discomfort in the abdomen and suprapubic area (three patients), and

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Table 1. Summary of the primary GU lymphoma cases from two tertiary Hospitals in the Western region of Saudi Arabia (n=11)

	Age (years)/ Gender	Presentation	Site of Involvement	Radiology	Pathology Diagnosis	Treatment	Outcome	Follow-up
1	40/Male	Suprapubic pain	Urinary Bladder	Raises the possibility of lymphoma	High-grade lymphoma	N/A	N/A	N/A
2	36/Female	Mesenteric mass	Left ureteric mass	Highly suggestive of lymphoma	High-grade B-cell lymphoma, stary-sky pattern	Received 4 cycles R-CHOP, post auto BMT after that	Relapsed after 6 weeks of BMT. On palliative support	4 months
3	71/Male	Vague abdominal pain	Left testis and spermatic cord	Did not suspected lymphoma	DLBCL	R-CHOP	PET scans show no relapsing lymphoma	60 months
4	24/Male	Severe abdominal pain, vomiting, diarrhea	Left testicular mass	Significant increased vascularity of the left testis	B-ALL	N/A	N/A	N/A
5	58/Male	Hematuria	Urinary bladder mass	Thickening of right bladder wall	DLBCL	R-CHOP	Remission state	21 months
6	47/Female	Suprapubic pain	Urinary bladder mass	Urinary bladder mass	low-grade B-cell lymphoma, favor MALT	Bendamustine and Rituximab	Remission state	28 months
7	55/Female	Hematuria	Urinary bladder mass	Urinary bladder mass	MALT	N/A	N/A	N/A
8	38/Male	Urgency & frequency of urination	Prostate	Large irregular prostatic mass	NHL, B-cell phenotype	N/A	N/A	N/A
9	48/Male	Frequency urination & hematuria	Prostate	N/A	DLBCL	R-CHOP	Remission state	13 months
10	36/Male	Testicular mass	Right testis	Did not suspected lymphoma	NHL, High-Grade	N/A	N/A	N/A
11	62/Male	Testicular mass	Left testis	Did not suspected lymphoma	DLBCL	R-CHOP	Remission state	16 months

DLBCL: Diffuse large B-cell lymphoma; B-ALL/LBL: B-Acute lymphoblastic leukemia/lymphoma; MALT: mucosa-assisted lymphoid tissue; NHL: Non-Hodgkin lymphoma; BMT: bone marrow transplant; BM: Bone marrow; CNS: Central nervous system; R-CHOP: cyclophosphamide, doxorubicin, prednisone, rituximab, and vincristine; NA: Not available.

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difficulty in passing urine (one patient). The testis was impacted in (4 cases, 36%) followed by urinary bladder (4 cases, 36%), prostate (2 cases, 18%), and ureter (1 case, 9%). Lymphoma was suspected clinically in two cases based on characteristics observed in radiology studies. One case of urinary bladder mass showed by Magnetic Resonance Imaging (MRI) an infiltrative process-involving wall of the urinary bladder and adjacent rectum including the periaortic area and great vessels raises the possibility of lymphoma. Another case of the ureteric mass showed by CT scan was an infiltrative enhancing soft tissue mass involving the mesentery and retroperitoneum with multiple similar lesions in the adjacent fat tissue. This appearance was highly suggestive of lymphoma. None of these patients was noted to have human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS). Out of the total 11 cases, one was diagnosed on resection specimen of which was orchiectomy. Others were pathologically confirmed on core needle biopsies. Lymphoma subtypes observed were DLBCL (4 cases, 36%) (**Figure 1A, 1B, 1E and 1F**); MALT lymphoma (2 cases, 18%); B-ALL/LBL (1 case, 9%) (**Figure 1C and 1D**); high-grade B-cell lymphomas (3 cases, 27%) one of them show morphology of Burkitt-like or stary-sky like pattern large cell type, and a case of high-grade lymphoma, unclassifiable (1 case, 9%). Ki-67 proliferative index in cases of DLBCL ranged from 50% up to 70%. In cases of low-grade MALT lymphoma, the Ki-67 index was less than 20%. Cases of high-grade lymphomas had a proliferative index exceeding 95%. The case diagnosed with LBL were of B-subtype, with strong TdT nuclear staining and high proliferative index. Standard therapy was administered to four DLBCL patients, entailing the administration of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP). All of them were on remission status, with the longest duration of follow-up among them lasting for 21 months. One case diagnosed with MALT lymphoma was treated with Bendamustine and Rituximab and was in remission for 28 months follow-up. One of the three cases diagnosed with high-grade B-cell lymphoma with a stary-sky pattern received four cycles of chemotherapy and got an auto bone marrow transplant after that. She relapsed after six weeks of transplant clinically and radiologically. She was under pallia-

tive support, and then the patient lost follow-up. Among all patients mean follow-up duration was 15.8 months (range from 4 to 60 months). The overall 2-years survival rate was 58% during follow-up years. All cases along with clinical and histopathological findings are summarized in **Table 1**.

Discussion

Despite the lack of any structured lymphoid tissue in the urinary tract, primary GU lymphomas may be derived from lymphoid cells that are drawn to the area due to recurrent infections. The use of antibiotics particularly in the case of MALT-associated lymphomas, has shown regression results of some cases, thereby supporting this hypothesis. Moreover, the theory stated above could be backed up by the fact that bladder lymphomas are more prevalent in women compared to men, possibly due to women having a higher incidence of cystitis than men. Additionally, it was observed that the bladder had a greater occurrence of MALT-associated lymphoma, a type of lymphoma frequently linked with bacterial infections [4]. Most cases reported in the published series were related to kidney and testis. A higher number of lymphomas were found in the prostate compared to the bladder. This is probably due to a higher occurrence rate of prostate biopsies instead of an increased probability of developing lymphoma in this location [2]. Distinguishing between primary and secondary involvement of lymphoma in extra nodal sites remains a challenging issue. The criteria suggested by Krol et al. [5] were utilized in conducting this study. This stated that if the extra nodal component is the primary clinical indicator, then any lymphoma that initially presents at an extra nodal location should be classified as such even if the disease has metastasized/disseminated. Adopting these criteria in our study was important as an inclusion criterion.

Despite their rarity, testicular lymphomas are among the most frequent lymphomas affecting the genitourinary system. DLBCL is the most known subtype raised in the testis [6]. A palpable testicular mass is a typical presentation of primary testicular lymphoma. In recent years, the average age of patients diagnosed with primary testicular lymphoma appears to have moved towards a comparatively younger age

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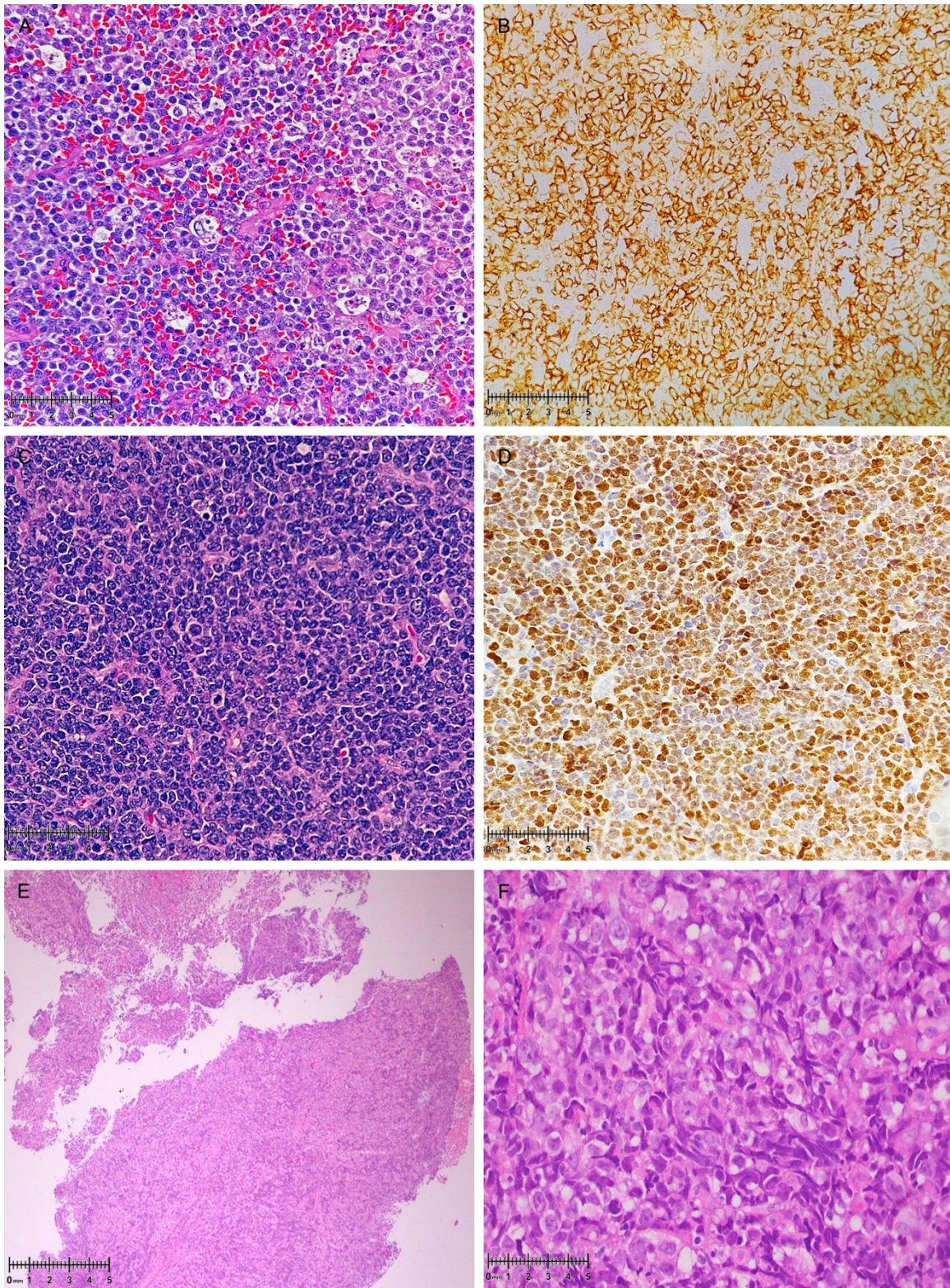


Figure 1. Histopathology examination by hematoxylin and eosin stain (H&E). A: Testicular mass with effacement of tissue architecture by diffuse infiltrate of large atypical lymphoid cells, note the stary-sky appearance (H&E; 20 \times). B: Diffuse and strong CD20 expression in the case of DLBCL (40 \times). C: Microscopic evaluation of B-ALL testicular mass composed of lymphocytic proliferation ranging from small to medium-sized primitive cells (H&E; 20 \times). D: Immunohistochemical staining showed strongly positive TdT in the B-ALL case (40 \times). E: Low-power magnification of bladder tissue biopsy infiltrated by tumor cells (H&E; 2 \times). F: Large atypical lymphoid cells arranged in a diffuse growth pattern consistent with diffuse large cell lymphoma of urinary bladder (H&E; 40 \times).

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range [7]. This finding could be partially caused by the increased prevalence of HIV/AIDS in younger individuals who have testicular lymphoma [8]. It is common for testicular lymphomas to be misdiagnosed as germ cell tumors, specifically seminoma. It is essential to correctly identify the type of tumor as treatment modalities vary significantly. Testicular lymphomas are identified by neoplastic lymphoid cells forming solid sheets that obliterate the testicular parenchyma. In many cases, an identifiable feature is the irregular clustering and grouping of tumor cells, which results in the expansion of seminiferous tubules. However, infiltration in seminiferous tubules is an infrequent occurrence. Advanced cases show micro-invasion of adjacent structures, such as epididymis and paratesticular tissue. None of the cases in our series were found to have Intratubular germ cell neoplasia, as reported by other publications [7, 9]. An aggressive treatment approach is usually necessary for managing patients with testicular lymphoma due to the daunting challenges and poor prognosis associated with this condition [8, 10, 11].

Lymphomas that affect the prostate gland are uncommon, representing less than 0.1% of extranodal lymphomas. Obstructive symptoms were observed in most patients. However, some are asymptomatic, but they may still be diagnosed after undergoing an abnormal digital examination and subsequent biopsy [12]. Due to the lack of lymphoid tissue in the normal prostate gland, some authors have previously questioned the existence of primary extranodal prostatic lymphoma. The existence of primary prostatic lymphomas has been proven through the identification of sporadic rudimentary lymphoid aggregates, which lead to occurrences of extramedullary hematopoiesis and lymphoma solely in prostate confined without involvement of pelvic or retroperitoneal lymph nodes [13]. Most lymphomas affecting the prostate are non-Hodgkin's lymphomas, and they tend to be mainly of B-cell origin. The most frequently observed subtype in one series was DLBCL, followed by CLL/SLL and follicular lymphoma, respectively [2]. Cases of MALT and mantle cell lymphoma arising primarily in the prostate have also been documented by other authors [14, 15]. Most of these patients have poor overall survival rates, as they typically do not survive beyond 3 years of follow-up. Some

studies indicate that prostatectomy alone may not yield optimum results, however, adding adjuvant chemoradiation therapy could possibly enhance the outcome [13, 16].

Primary urinary bladder lymphoma is not commonly found. The pathophysiology behind bladder lymphomas remains unclear as they lack lymphoid tissue and germinal follicle cells. The presence of chronic cystitis presents up to 40% of reported cases indicating that lymphomas may arise in the context of prolonged inflammation resulting from cystitis. Hematuria and recurrent urinary tract infections are the most common symptoms observed in bladder lymphomas. Primary bladder lymphoma is typically observed as a solitary mass on the dome or lateral walls during cystoscopy examination [3]. Thus, the first impression from clinical examination could be either a urinary tract infection or urothelial carcinoma. There is no sex predilection, while some authors have reported a higher number of females population. The predominant histologic subtypes of lymphoma observed included DLBCL, mantle cell lymphoma, and follicular lymphoma. While our study primarily focused on bladder lymphomas, it's worth noting that we did observe only one case of MALT lymphoma. This occurrence may be attributed to the limited number of lymphomas affecting the bladder in our study, which considered a major limitation of the study. The optimal treatment strategy for bladder lymphomas is a subject of ongoing debate. While the available management choices encompass chemotherapy, radiation, and surgery; chemotherapy is presently the preferred option as it addresses not only detectable tumors but also potential early-stage disease [17]. Lymphomas affecting the ureter are exceedingly uncommon, with only a handful of published cases reported. Obstructive symptoms are commonly observed in patients, and they subsequently experience the development of unilateral hydronephrosis. While most cases occur unilaterally, there has been a documented instance of primary bilateral ureteral lymphoma [18]. While our study's scope is confined to two institutional data, the wide range of lymphoma subtypes and the various sites of involvement observed in this cohort emphasize the significance of including lymphoma or plasmacytoma as potential considerations in the differential diagnosis of urinary tract and male genital organ tumors.

Studies had suggested that surgical resection may prove advantageous for PUTL patients. This is significant considering that chemo and radiation therapy are the standard treatments for nodal disease [19]. It is possible that in most patients, surgery was performed primarily for diagnostic reasons, although there is a chance that debulking may improve their chances of survival. It is worth mentioning that a study conducted by Kim and colleagues also supports the notion that surgery is beneficial for intestinal lymphoma [20]. On the other hand, a different study reveals that MALT lymphoma of the urinary bladder can be highly responsive to localized treatments, and even the intake of antibiotics can cause tumor regression [21]. Although surgery is not a common practice for MALT lymphomas, the analysis conducted was variable and as DLBCL remains the dominant type, any benefits derived from surgical intervention should be applicable to all cases [22]. Out of the three most common GU pathologic subtypes that were analyzed, DLBCL showed the poorest prognosis, while patients with MALT lymphoma had the most favorable prognosis. Better survival was also found to be associated independently with the female gender. Patients with PUTL also exhibit prognostic significance based on their age categorization according to International Prognostic Index (IPI) by National Comprehensive Cancer Network (NCCN) [23].

Conclusion

In our study, we found that there is no correlation between primary GU lymphoma and immune status or HIV infection. DLBCL is the most common histological type in GU region followed by MALT lymphoma. Histopathologic examination is considered the gold standard in diagnosing primary lymphoma of the GU region. Ancillary studies such as immunohistochemistry stains are considered valuable techniques for determining lymphoma subtype and cells of origin which can provide important prognostic information. Utilizing emission tomography and conducting bone marrow examination are crucial steps for excluding the presence of systemic disease. Our study offers site-specific outcome information and emphasizes the diagnostic challenges encountered in lymphomas affecting the GU system, contributing to the existing findings in previously published case series.

Disclosure of conflict of interest

None.

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