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Diffuse Large B-Cell Lymphoma Transformed from Mucosa-Associated Lymphoid Tissue Lymphoma Arising in a Female Urethra Treated with Rituximab for the First Time

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Key Words
Urethra · NHL · Chemotherapy · Malignant lymphoma · Female urethra · CHOP-R chemotherapy

Abstract
A 30-year-old female patient presented to the gynecology clinic with a small (painless) swelling at the urethral orifice. She underwent surgical excision of the lesion. Pathological examination revealed non-Hodgkin's lymphoma of diffuse large B-cell type and mucosa-associated lymphoid tissue type, stage IE. The patient refused radiotherapy. Accordingly, we started CHOP-R chemotherapy. She received a total of 6 cycles of CHOP and 8 cycles of rituximab. Patient follow-up was done 3 months later through CT scan and cytoscopy confirming the complete remission. The patient has been disease-free for 4 years. We reviewed 26 cases of this rare entity reported previously.

Introduction

Lymphoma constitutes approximately 7% of all urogenital neoplasm [1]. The most frequent finding is of bladder involvement secondary to nodal disease [2]. Although cases of urethral lymphoma have been reported, the majority involve tumors arising in mucosa-associated lymphoid tissue (MALT) [3, 4]. Primary tumors arising from the urethra remain case reportable. Of the cases of primary urethral lymphoma that have

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been described, 19 cases have been reported in female patients and 7 cases in men, 1 of which was associated with HIV infection [1, 5–7]. Limited clinical experience has resulted in uncertainty concerning the most appropriate form of therapy for this malignancy.

Case

In February 2007, a 30-year-old woman presented to the gynecology clinic with a small painless mass at the urethral orifice. She underwent surgical excision of the lesion and histopathology revealed a mixture of acute and chronic inflammation consistent with urethral carbuncle. Two months later she presented with a hyperemic small swelling at the site of the excision. She underwent re-excision; and a mass from the urethral mucosa was biopsied. Pathologic examination of the specimen revealed a diffuse monotonous proliferation of malignant lymphoid cells of mostly large cell size; some of which are medium size and have a monocytoid appearance. The urethral mucosa above the infiltrate is focally infiltrated by malignant lymphoid cells (**fig. 1**, **fig. 2**). The deep component of the tumor infiltrates the glandular epithelium of the urethra (lymphoepithelial lesion); a feature strongly suggestive of MALT lymphoma (**fig. 3**). Immunohistochemistry for cytokeratin highlights these lesions (**fig. 4**, **fig. 5**). Immunocytochemistry studies demonstrated that the tumor cells have a strong positive reaction to CD45 (leukocytic common antigen, LCA) and CD20 (**fig. 6**).

For staging workup she underwent chest, abdomen and pelvis CT which revealed no mediastinal lymphadenopathy, no lung focal lesion, a 3-mm cystic focus on the right lobe of the liver, normal spleen, pancreas and kidney, and no abdominal or pelvic lymphadenopathy. There is a slight apparent localized thickening of the bladder neck. MRI of the hepatic lesion revealed a simple benign cyst. Blood workup including LDH, ESR, β_2 microglobulin, HIV, hepatitis and STD profile was done and all were normal. Bone marrow examination was negative. Upper gastrointestinal endoscopy did not reveal any MALT-associated lesions. Therefore, the final diagnosis was non-Hodgkin's lymphoma of female urethra, diffuse large B-cell, possibly transformed from MALT lymphoma, stage IE according to Cotswolds modification of the Ann Arbor staging system.

The patient was offered localized radiotherapy. She refused this modality after being counseled about the possible side effects including the high possibility of infertility. Accordingly, we offered her chemotherapy (R-CHOP regimen including, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone). The patient underwent staging reassessment with CT scan and cytoscopy after 4 chemotherapy cycles. Multiple biopsies revealed a complete remission. A total of 6 cycles of CHOP and 8 cycles of rituximab were completed. Patient follow-up was done 3 months later with CT scan and cytoscopy confirming the complete remission. The patient has been free of disease for 4 years.

Discussion

Caruncles are the most common lesions of the female urethra; they are inflammatory nodules that arise at the urethral meatus in postmenopausal women [8]. Urethral caruncles usually arise from the posterior lip of the urethral meatus. The lesion is considered to be neither neoplastic nor preneoplastic, but probably results from local trauma or inflammation. However, carcinoma (1.6%) and Bowen's disease (0.8%) are extremely rare and have been noted in 2.4% of patients with a clinical diagnosis of urethral caruncle. Macroscopically, a caruncle is a nodular or pedunculated erythematous lesion that may bleed easily.

Lymphoma of the female urethra, on the other hand, is an exceedingly rare condition. The literature describes only 27 cases (19 of them were female and 8 were male; **table 1**). All were non-Hodgkin's lymphoma [9–13]. The age distribution ranged from 31 to 90 years with a mean of 67 years. The most common reported complaints

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were polyp, dysuria, urethral mass, irregular vaginal bleeding, gross hematuria, pain, urinary retention, carbuncle, and genital itching [13–17].

Four cases have been reported as having a painless mass at the urethral meatus resembling a caruncle as in our own case [9, 10]. Two cases were treated with radiotherapy, one case was treated with excision, and the last was treated palliatively. Our case is the first urethral lymphoma case treated with chemotherapy (CHOP-R). Another male urethral case was treated with CHOP without rituximab. In that described case of primary lymphoma of a male urethra, the patient remained alive and in complete remission 2 years after surgical removal and 6 courses of CHOP chemotherapy. It has been reported that prognosis for short-term local control of the urethral tumor with chemotherapy is excellent; recent cases show a short-term control rate of 100% [18].

Conclusion

There is no universally accepted treatment scheme for these tumors. Although, several authors have reported reasonable success using excision, radiotherapy, chemotherapy, or combinations. Although the number of cases reported was very small and the follow-up period was short in all cases, local therapy including excision or external beam radiation with/without chemotherapy showed a good outcome in patients with local or locally invasive tumor. However, patients with disseminated disease showed a poor prognosis regardless of the kind of initial treatment. Accordingly, in patients with unfavorable histology or disseminated disease, early intensive chemotherapy is recommended. Use of the chemotherapy regimen CHOP-R seems to be a reasonable treatment option. For patients without bulky disease, 6–8 cycles of CHOP-R without radiotherapy have been shown to be an equally effective alternative as reported in our case [19]. Therefore, we recommend that any caruncle-like lesion should be evaluated with a suspicion of a malignant tumor unless proved otherwise.

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Table 1. Summary of reported cases of primary urethral lymphoma

No.	First author	Year	Age years	Sex	Chief complaint	Localization	Treatment	Outcome	Observation period
1*	Grabstald [16]	1966	Unknown	F	Unknown	Unknown	Radiation	NED	9 months
2*	Nabholtz [10]	1989	51	F	Urethral polyp	Localized urethral	Chemo + exci	NED	120 months
3*	Pak [11]	1980	83	F	Dysuria	Localized urethral	None	Dead	Unknown
4*	Simpson [12]	1990	76	F	Urethral mass	Localized urethral	Excision	NED	24 months
5*	Vapnek [15]	1992	31	F	Irregular vaginal bleeding	Localized urethral	Chemo + radi	NED	9 months
6*	Kakizaki [20]	1994	63	M	Urethral mass	Localized urethral	Chemo + exci	NED	36 months
7*	Ohsawa [21]	1994	78	F	Dysuria, polyuria	Localized urethral	Chemotherapy	Unknown	Unknown
8*	Khatib [2]	1993	65	F	Irregular vaginal bleeding	Localized urethral	Excision	NED	24 months
9*	Atalay [19]	1998	76	F	Pain on urination, urinary tract tumor	Localized urethral	None	Dead	Unknown
10	Kurtman [22]	2001	32	M	Urinary retention	Localized urethral	Radiation	NED	15 months
11	Masuda [3]	2002	56	M	Gross hematuria	Localized urethral	Radiation	NED	21 months
12	Inuzuka [23]	2003	69	F	Dysuria, urinary tract tumors	Localized urethral	Exci + chemo	NED	6 months
13	Ryu [24]	2003	25	M	Dysuria, tumor palpable lump	Localized urethral	Chemotherapy	NED	67 months
14	Chuang [25]	2005	50	F	Caruncle	Localized urethral	Radiation	NED	14.5 months
15	Richter [18]	2007	48	M	Dysuria, meat hematuria eye	Localized urethral	Exci + chemo	NED	3 months
16*	Melicow [9]	1972	76	F	Caruncle, hematuria	Local infiltration	TUR + radi	NED	12 months
17*	Touhami [13]	1987	63	F	Genital itching, dysuria	Local infiltration	Chemotherapy	NED	48 months
18*	Selch [14]	1993	75	F	Irregular vaginal bleeding	Local infiltration	Radiation	NED	42 months
19*	Shimizu [26]	1997	82	F	Dysuria	Local infiltration	Chemo + radi	Dead	7 months
20*	Watson [27]	1949	62	F	Caruncle, spotting	Disseminated	Excision	Dead	5 months
21*	Allen [28]	1978	53	F	Caruncle	Disseminated	Palliative	Dead	2 months
22*	Chaitin [29]	1993	77	F	Genital mass, hematuria	Disseminated	Chemotherapy	NED	9 months
23*	Lopez [6]	1993	57	M	Dysuria, hematuria	Disseminated	Chemotherapy	Dead	3 months
24*	Rajan [30]	1995	57	M	Urinary retention, hematuria	Disseminated	Chemotherapy	NED	6 months
25	Dell'Atti [31]	2005	69	F	Dysuria, from thermal weight loss	Progressive systemic	Exci + chemo	Unknown	Unknown
26	Muraoka [32]	2009	90	F	Dysuria	Localized urethral	Exci + radi	NED	14 months
27	Al Zahrani	2011	30	F	Caruncle		Chemotherapy	NED	

Exci = Excision; chemo = chemotherapy; TUR = transurethral resection; radi = radiation; NED = no evidence of disease. *Another hospital death.

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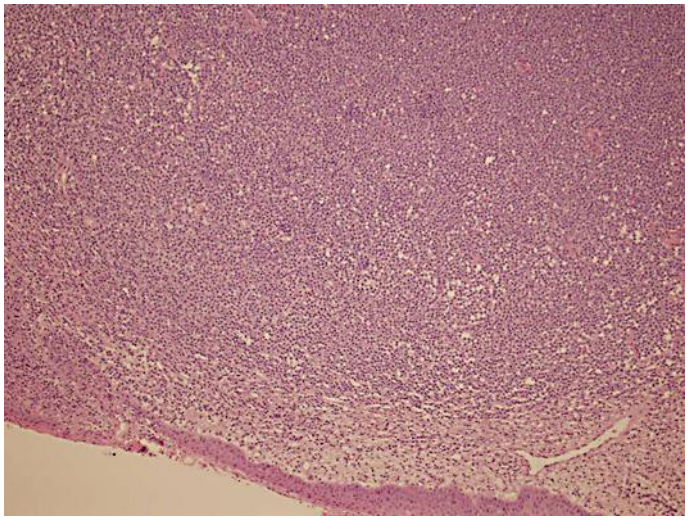

Fig. 1. Diffuse monotonous proliferation of malignant lymphoid cells, the urethral mucosa above the infiltrate is focal (hematoxylin and eosin, ×100).

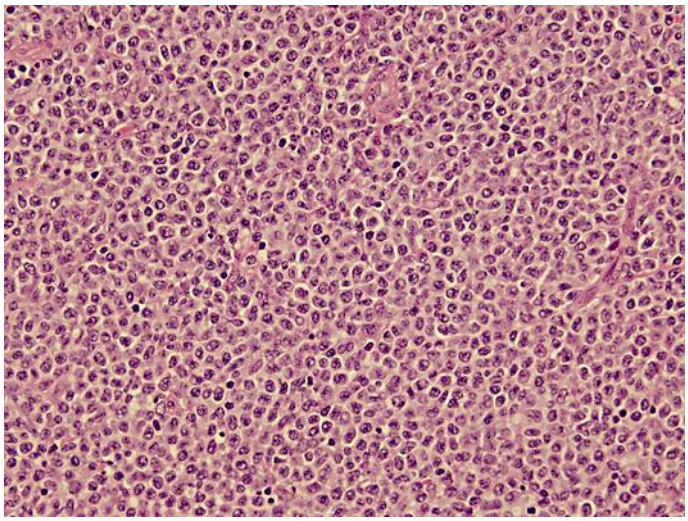

Fig. 2. Diffuse proliferation of malignant ltmphoid cells (hematoxylin and eosin, ×400).

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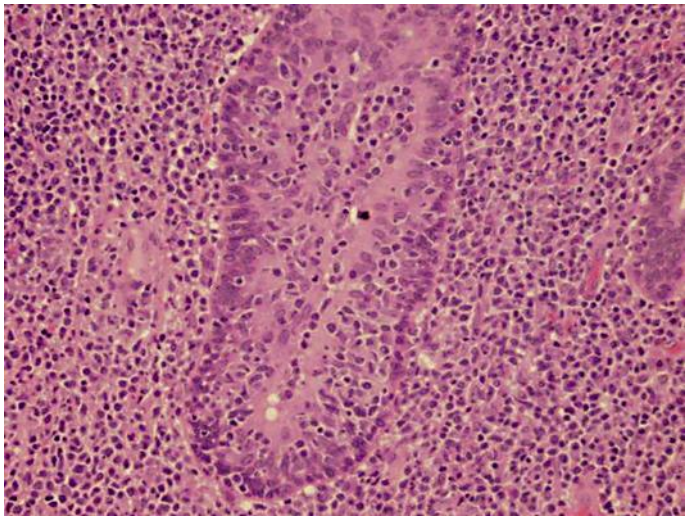

Fig. 3. Glandular epithelium of the urethra (lymphoepithelial lesion), a feature strongly suggestive of MALT lymphoma (hematoxylin and eosin, ×200).

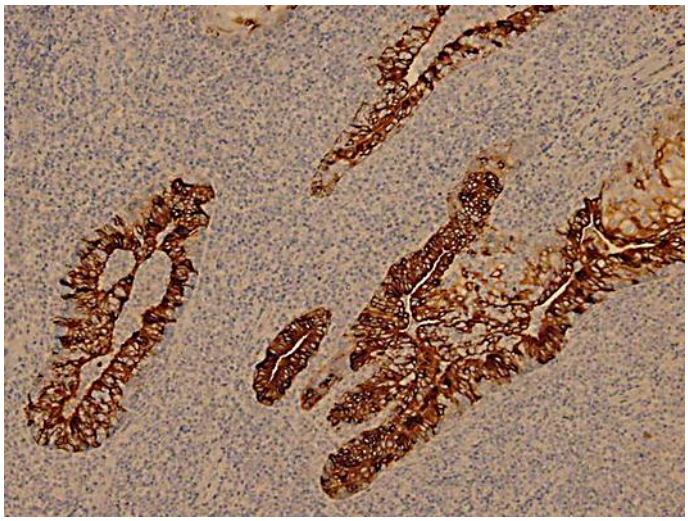

Fig. 4. Image highlights lymphoepithelial lesions; immunohistochemistry stain with cytokeratin (Dako; ×200).

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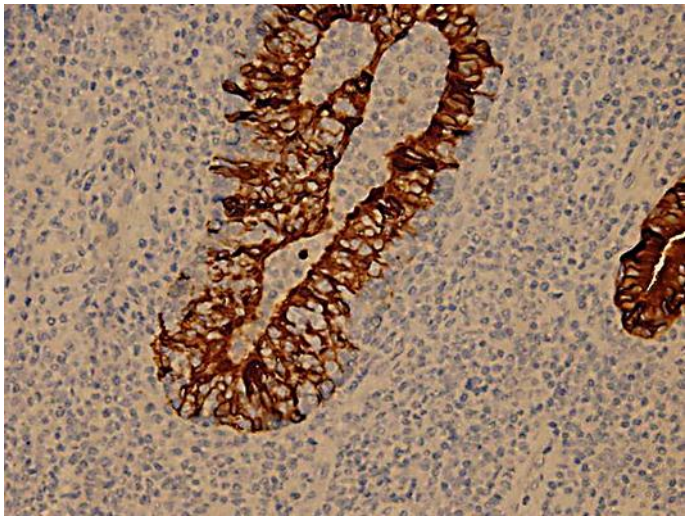

Fig. 5. Image highlights lymphoepithelial lesion; immunohistochemistry stain with cytokeratin (Dako; ×400).

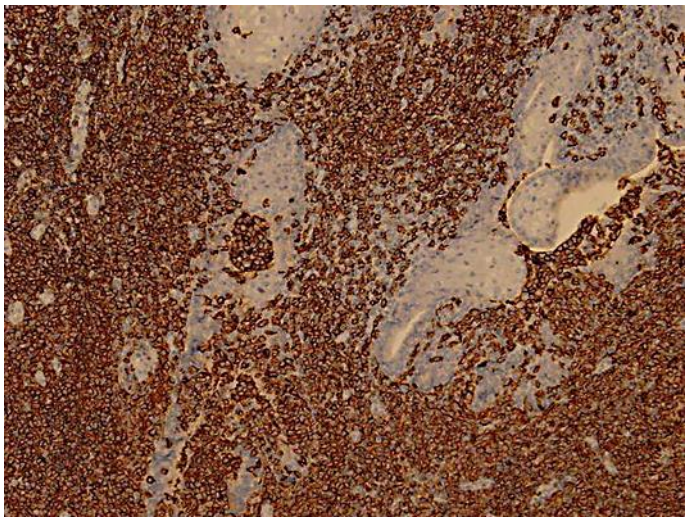

Fig. 6. Image highlights lymphoid cells with positive reaction to CD20 (Dako; ×200).

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