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Lymphoepithelioma Like Carcinoma of the Urinary Bladder: Two Incident Reporting Studies

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Abstract

We report two cases of lymphoepithelioma like carcinoma of the urinary bladder. Such cases are rare and the purpose of this study is to combine both of them presented in AGIOS DIMITRIOS General Public Teaching Hospital of Thessaloniki and the English literature in order to find the right treatment for each type of LELCB (pure, predominant or focal). Currently we cannot define a specific therapeutic guideline for patients with LELCB. It is important to expand our knowledge and experience regarding this type of tumor. More studies are needed to better understand this rare disease and to more precisely define diagnostic and therapeutic strategies.

Keywords: Lymphoepithelioma; Urinary bladder; Types; Literature; Treatment

Abbreviations

WHO: World Health Organization; EBV: Epstein-Barr virus; LELCB: Lymphoepithelioma-like Carcinoma of the Urinary Bladder; LELC: Lymphoepithelioma-like Carcinoma; ADC: Apparent Diffusion Coefficient; EMA: Epithelial Membrane Antigen; CK7: Cytokeratin 7; CK20: Cytokeratin 20; TUR: Transurethral Resection; TURBT: Transurethral Resection of Bladder Tumor; MVAC: Methotrexate, Vinblastine, Adriamycin and Cisplatin; GC: Gemcitabine plus Cisplatin

Introduction

Lymphoepithelioma is a type of poorly differentiated nasopharyngeal carcinoma characterized by prominent infiltration of lymphocytes in the area involved by tumor. Lymphoepithelioma is also known as "class III nasopharyngeal carcinoma" in the WHO classification system. It has a high tendency to metastasize and is responsive to radiotherapy. Most cases are associated with Epstein-Barr virus (EBV) infection [1]. Lymphoepithelioma-like Carcinomas are carcinomas that arise outside of the nasopharynx, but resemble a lymphoepithelioma histologically [2]. According to the WHO classification criteria, LELCB is defined as a subtype of undifferentiated carcinomas [3]. Lymphoepithelioma-like carcinomas may be found in almost any epithelial organ, including the lung, thymus, breast, colon, endometrium, prostate, and skin [4], as well as urinary bladder, trachea, esophagus, stomach, salivary glands, vulva [5]. They may coexist with the conventional adenocarcinomas of the above mentioned organs and therefore they are classified according to the percentage of lymphoepithelioma component within the tumor. Therefore three types of LELC are described: pure (100%), predominant (> 50%), or focal (< 50%) [6]. These three types were defined in 1994 by Amin et al and they determine the patient's prognosis [3].

LELC of the Urinary Bladder was first reported in 1991 by Zukerberg et al [3]. They are uncommon as they account of 0.4% - 1.3% of all Bladder carcinomas [7]. They may coexist with the conventional urothelial carcinoma [6]. Epstein-Barr virus (EBV) is associated with lymphoepithelioma or LELC of several tissues (lung, stomach and salivary glands), except the bladder [3]. We herein report two cases of LELCB (male and female patients). The histological examination showed pure lymphoepithelioma like carcinoma in the female patient and predominant lymphoepithelioma like carcinoma in the male patient. We performed partial cystectomy and the patients are under close observation.

Cases Presentations

Case 1

A 34-year old female presented with episodic macroscopic hematuria. There was associated

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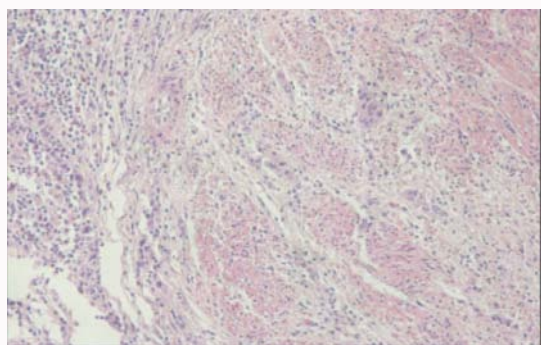


Figure 1: Lymphoepithelioma-like carcinoma (LELC) in urinary tract is a rare malignancy, named for its resemblance to nasopharyngeal undifferentiated carcinoma or lymphoepithelioma (x40).

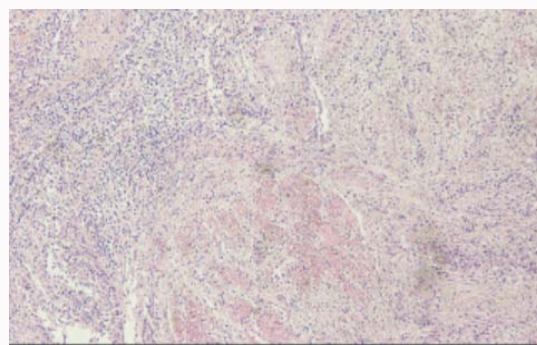


Figure 2: Lymphoepithelioma-like carcinoma (x200).

dysuria.

Case 2

A 68-year old male presented with episodic macroscopic hematuria for 1-week. There was no associated dysuria but the patient had a past history of urothelial carcinoma of the urinary bladder six months ago.

In both cases: Physical examination, vitals, and basic laboratory workup were unremarkable. Urine cytology revealed the presence of hematuria and the cytology was reported as suspicious for malignancy.

- Cystoscopy was performed which showed

Case 1: the presence of a 5 cm × 4 cm × 3 cm lymphoepithelioma like carcinoma in the urinary bladder stage III.

Case 2: the presence of a 4cm x 4,5cm x 2,5cm lymphoepithelioma like carcinoma in the urinary bladder stage III.

Results

Partial cystectomy was performed and the histological examination showed pure lymphoepithelioma like carcinoma in the female patient and predominant lymphoepithelioma like carcinoma in the male patient (Figure 1 and 2). Microscopically the tumor consisted of undifferentiated round or spindle cell admixed with lymphoid tissue. The tumor cells arranged in syncytial sheets/nests with abundant mixed inflammatory cells (lymphocytes, histiocytes, eosinophils). The surgical margins and dissected lymph nodes were tumor-free.

Discussion

Recently, measuring ADC values has been suggested to be helpful in diagnosing bladder tumors. Regardless, though LELCB is a rare tumor, measuring ADC values may be useful in predicting the histopathological characteristics of such bladder tumors [3]. Histologically, these tumors are composed of epithelial cells arranged in sheet with a syncytial aspect, vesicular nuclei, prominent nucleoli, and pronounced lymphoid reaction. It is possible that this kind of tumor can be associated with any other type of bladder cancer and at any stage [8]. Immunohistochemistry is essential, showing the epithelial component (membrane epithelial antigen (EMA), CD46v6, and cytokeratin cocktail antibodies (AE1/AE3), cytokeratin 7 (CK7), and cytokeratin 20 (CK20)) and lymphocyte component (CD21, CD20, CD79a, CD45RO, CD68, and D33). The lymphoid population is a mixture of T and B lymphocytes, with T-cell predominance [8]. Also, the immunohistochemical profile of LELCB seems to include

positivity for high molecular weight CK34bE12, CK7, and p63, coupled with negativity for CK20 in most cases. The predominance of lymphoepithelial component might be a good prognostic factor [9]. Owing to the rarity of LELCB, there is no treatment guideline for these patients. Treatments of LELCB often consist of transurethral endoscopic resection, or partial cystectomy, or radical cystectomy. Cisplatin-based chemotherapy plus radiation therapy is usually the adjuvant treatment [9]. Most pure subtype tumors had been treated with TUR regardless of the tumor stage and had been treated with adjuvant treatment. This observation raises the possibility of bladder preservation inpatients with pure and predominant subtypes. This positive prognosis is overshadowed when there are patterns associated withurothelial carcinoma [8]. Comparing treatment modality, 50% of the cases utilized one treatment modality only with radical cystectomy being the most common (58.6%) followed by TURBT (30.0%), partial cystectomy (7.1%), and intravesical chemotherapy (1.4%) with outcomes of no evidence of disease (55.7%), died of disease (12.9%), alive with metastasis (10.0%), and died without disease (7.1%). Of the multi-modality treatments, primary treatments were diverse and included TURBT (49.9%), radical cystectomy (41.0%), partial cystectomy (6.0%), intravesical chemotherapy (1.5%), chemotherapy (0.8%), and radiation therapy (0.8%). Secondary treatments included chemotherapy (51.8%), radiation therapy (28.2%), TURBT (7.1%), intravesical chemotherapy (7.1%), radical cystectomy (4.7%), and thermal ablation (1.2%). Outcomes for those receiving multi-modal treatments include no evidence of disease (67.2%), alive with metastasis (10.5%), died without disease (9.0%), and died of disease (7.5%) [10]. Comparing surgical resection methods, TURBT alone has the lowest disease-free survival rate (33.3%) when compared to any combination therapy (67.9%) TURBT alone also carries the highest mortality rate (23.8%) when compared to any combination therapy (7.1%). Radical cystectomy is associated with the highest disease-free survival rate at 67.8% and is significant when compared to TURBT alone at 33.3% but not significant when compared to partial cystectomy at 50% [10]. Systematic chemotherapy treatments utilized are varied with 24 cases documenting detailed regimens. Of those, eight cases specified MVAC treatments while 16 cases specified GC treatments. Neoadjuvant chemotherapy was administered in 4.3% of cases with an average disease-free survival of 41 months and did not significantly impact outcome. Comparing subtypes of LELC, the treatment regimens reported did not significantly differ; of those with pure and predominant LELC, 71.0% and 75.0% had no evidence of disease, respectively, while only 31.6% of mixed LELC patients had the same outcome. In addition, patients who underwent radical cystectomy had the highest disease-free survival (67.8%) when compared to partial cystectomies (50%) or TURBT

only (33.3%). However, patients receiving TURBT combined with any type of secondary treatment have a 71.1% disease-free survival rate [10]. LELC of the bladder is a rare cancer that most often presents with painless hematuria occurring in older males [11]. By the time of presentation, most LELCs have invaded the muscularispropria but have not metastasized outside of the bladder. Even though LELC in other organ systems has been shown to be associated with EBV, no case of LELC in the bladder has been associated with the presence of EBV. The subtypes of LELC appear to significantly impact outcome, as disease-free survival is higher in predominant and pure LELC than mixed LELC. Highest mortality is mixed LELC followed by predominant and pure LELC and this could suggest that LELC itself is not as aggressive as high-grade urothelial carcinoma [10]. It would be convenient to define whether the pure subtype increased Lymphoepithelioma-Like Bladder Carcinoma survival rates is related only because of the histology or because that subtype has received adjuvant treatment most frequently [8]. With survival analysis carried out and according to the authors of literature, it seems that conservative treatment should be considered in cases of pure and predominant subtypes [8]. As for treatment impacting outcome, TURBT alone should not be recommended, as it is associated with both lowest disease-free survival and highest mortality rate. Radical cystectomy is associated with the highest disease-free survival rate, whereas partial cystectomy was only utilized as the main surgical resection method in eight cases its impact is unknown [12]. As for neoadjuvant chemotherapy, it was administered in six cases and while it had a longer disease survival, it was not significant, perhaps also due to the small sample size. As for chemotherapy regimen, it appears to have evolved over time and without significant difference as all eight cases of MVAC was before 2003 and all 16 cases of GC were after [10].

Conclusion

Since bladder carcinoma is more susceptible to both chemotherapy and radiotherapy than ordinary urothelial carcinoma, radical cystectomy may not be necessary for all patients with muscular invasive bladder lymphoepithelioma [13]. Therefore, pathological information may be useful in selecting patients suitable for bladder maintenance treatment [14]. On the other hand, the seemingly more aggressive nature of focal urinary bladder lymphoepithelioma cancer suggests that these patients are most likely treated better with radical cystectomy and adjuvant treatment [15].

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