

Lymphoepithelioma-like carcinoma of the urinary bladder: A case report and review of systemic treatment options

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Abstract Lymphoepithelioma-like carcinoma (LELC) of the urinary bladder is a rare variant, which can occur in a pure form or in conjunction with transitional cell carcinoma. Owing to the scarcity of reported cases, the optimum treatment is yet to be defined, although the benefits of chemotherapy are increasingly recognised. We present a case of a 64-year-old man with pure LELC, treated with trans-urethral resection of the bladder tumor (TURBT) and primary gemcitabine and platinum-based chemotherapy. He remained free of disease at six-month follow-up cystoscopy. The case adds to the growing evidence for the efficacy of chemotherapy, coupled with TUR, as part of a bladder-preserving treatment option for LELC.

Key Words: Bladder, bladder-preserving, chemotherapy, lymphoepithelioma-like carcinoma

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INTRODUCTION

Lymphoepithelioma describes an undifferentiated nasopharyngeal carcinoma, characterised by a prominent lymphoid infiltrate. Tumors with similar histological appearance, termed lymphoepithelioma-like carcinomas (LELC), have been reported at other sites, including the stomach, cervix, lung, hepatobiliary tract and ovary.

LELC of the urinary bladder was first described by Zukerberg in 1991, and represents between 0.4-1.3% of all bladder cancers.^[1,2] Differentiation from transitional cell carcinoma (TCC) is important, since it has implications for prognosis and treatment. We present a case to raise awareness of these unusual tumors, and to add to the

emerging evidence for the use of primary chemotherapy in their treatment.

CASE REPORT

A 64-year-old man presented with a two-month history of haematuria. He was otherwise asymptomatic, a non-smoker for the previous 30 years with no significant occupational risk factors. Flexible cystoscopy demonstrated a mass within the bladder neck and a computed tomography (CT) scan showed no evidence of metastases or lymphadenopathy [Figure 1]. He underwent a trans-urethral resection of the bladder tumor (TURBT), and subsequent histological examination of the specimen revealed a high-grade T2 LELC with no conventional TCC present [Figures 2 and 3].

He received four cycles of gemcitabine and platinum-based chemotherapy. Gemcitabine was given at 1 g/m² on Days 1 and 8 of a 21-day cycle and cisplatin 70 mg/m² on Day 1 was replaced by carboplatin AUC5 on Day 1 for Cycles 2-4 because of ototoxicity. Biopsies from a repeat cystoscopy after the third cycle revealed only minimal nonspecific chronic inflammation with no malignancy remaining. He remains free of disease at six months' follow-up cystoscopy.

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Figure 1: A coronal computed tomography scan with contrast demonstrating a homogenous mass at the bladder neck. No metastases or lymphadenopathy were present

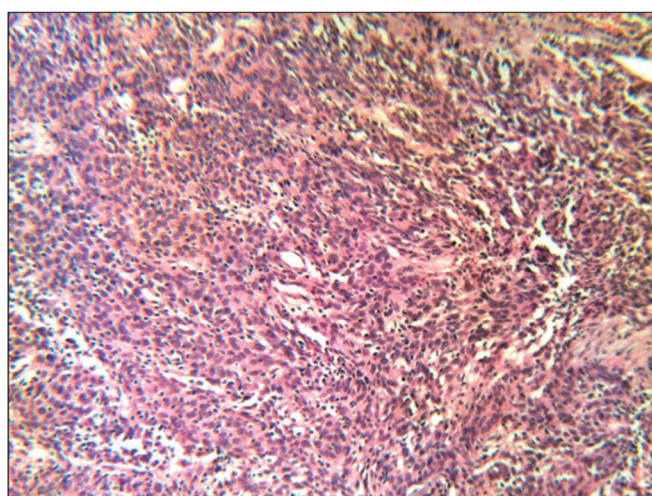


Figure 2: A high-power view of the specimen demonstrating pure LELC: A syncytial arrangement of malignant cells and many admixed lymphocytes

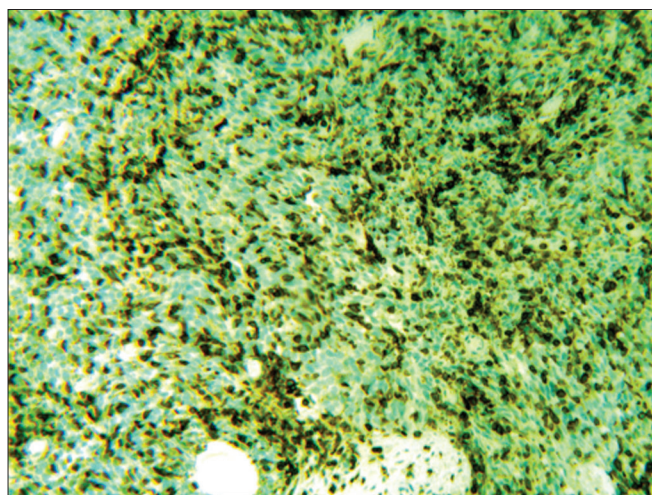


Figure 3: Immunohistochemical staining with leukocyte common antigen highlights the dense lymphocytic infiltrate within the tumor

DISCUSSION

Lymphoepithelioma-like carcinoma of the bladder is a rare variant, which is usually muscle-invasive at presentation.^[2] The most common presenting feature, haematuria, is the same as that for any bladder tumor, and it is typically diagnosed in the sixth to eighth decade of life.

It is characterised by a syncytial arrangement of undifferentiated tumor cells with prominent lymphocytic infiltration. It may occur in isolation, or in association with TCC. Amin *et al.*, described a classification system, determined by the percentage of LELC morphology within the tumor, characterising pure (100%), predominant (>50%) and focal (<50%) disease.^[3]

The differential diagnosis includes chronic cystitis, non-Hodgkin's lymphoma and poorly differentiated TCC, all of which may have similar histological appearances. Accurate diagnosis relies on identification of the characteristic morphology together with immunohistochemical staining. Stains are used to demonstrate both the lymphocytic (CD20, CD21, CD45RO, CD68, CD79a, D33) and epithelial (CK7, CK20, AE1, AE3, EMA, CD46v6) tumor constituents.

It is important to improve awareness of this subtype of bladder cancer, particularly amongst histopathologists, since differentiation has prognostic and therapeutic implications. When compared with TCC, the stage-specific prognosis for LELC is favourable, especially for pure disease.^[4]

However, the scarcity of reported cases has caused difficulties in defining the optimum therapy. Serrano *et al.*, conducted a pooled analysis of 56 patients and concluded that, whilst focal disease is more aggressive and requires a radical cystectomy, pure or predominant tumors are amenable to bladder-preserving treatment.^[5]

The benefits of chemotherapy are increasingly being recognised, even in infiltrative disease. In the Serrano study, patients with pure/predominant LELC who received systemic chemotherapy following TUR demonstrated a 100% disease-free survival, compared with 53% disease-free survival in those who did not, at a median follow-up of 34 and 25 months respectively [Table 1]. All the patients successfully treated with TUR and chemotherapy had invasive disease (T2) at presentation.

A variety of chemotherapy regimes have been used and, again, the limited number of reported cases hinders comparison. However, platinum-based agents, similar to those used in our case, have shown promising outcomes. Dinney *et al.*, used cisplatin as primary chemotherapy for three patients with

Table 1: An overview of primary therapy and outcomes for 33 patients with LELC, treated with TURBT

Reference	Subtype	Stage	Primary treatment	F/U	Outcome
<i>Dinney</i> ^[6]	Pu	T2	Chemotherapy	72	No disease
<i>Dinney</i> ^[6]	Pu	T2	Chemotherapy	60	No disease
<i>Dinney</i> ^[6]	Pu	T2	Chemotherapy	11	No disease
<i>Amin</i> ^[3]	Pu	T2	Chemotherapy	72	No disease
<i>Amin</i> ^[3]	Pu	T2	Chemotherapy	60	No disease
<i>Amin</i> ^[3]	Pu	T2	Chemotherapy	11	No disease
<i>Amin</i> ^[3]	Pre	T2	Chemotherapy	9	No disease
<i>Constantinides</i>	Pu	T2	Chemotherapy	34	No disease
<i>Lopez</i> ^[5]	Pu	T2	Chemotherapy	21	No disease
<i>Lopez</i> ^[5]	Pu	T2	Chemotherapy	47	No disease
<i>Chen</i>	NR	T2	Chemotherapy and BCG	10	No disease
<i>Constantinides</i>	Pu	T1	Intravesical chemotherapy	28	No disease
<i>Kruslin</i>	NR	T2	Intravesical chemotherapy	10	No disease
<i>Holgman</i>	Pu	T2	Radiotherapy	216	Death
<i>Zuckerberg</i> ^[1]	Pu	NR	Radiotherapy	NR	Not recorded
<i>Holgman</i>	Pu	T1	Radiotherapy	13	Death
<i>Holgman</i>	Pre	T3	Radiotherapy	21	Death
<i>Holgman</i>	Foc	T3	Radiotherapy	9	Death caused by malignancy
<i>Izquierdo-García</i>	Pu	T2	Radiotherapy	39	No disease
<i>Izquierdo-García</i>	Pre	T2	Radiotherapy	36	No disease
<i>Izquierdo-García</i>	Foc	T1	Radiotherapy	54	No disease
<i>Holgman</i>	Pu	T2	None	24	No disease
<i>Holgman</i>	Foc	T1	None	66	Death caused by malignancy
<i>Lopez</i> ^[5]	Pre	T2	None	22	No disease
<i>Lopez</i> ^[5]	Pre	T2	None	49	No disease
<i>Lopez</i> ^[5]	Pre	T2	None	25	Alive with metastases
<i>Lopez</i> ^[5]	Pre	T2	None	44	Death caused by malignancy
<i>Lopez</i> ^[5]	Foc	T2	None	3	Death caused by malignancy
<i>Lopez</i> ^[5]	Foc	T2	None	30	Death caused by malignancy
<i>Porcaro</i> ^[2]	Pre	T2	None	17	No disease
<i>Wrad</i>	NR	T1	None	NR	Not recorded
<i>Guresci</i>	NR	T3	None	11	No disease
<i>Yaqoob</i>	Pre	T2	Not recorded	NR	Not recorded

Pu: Pure; Pre: Predominant; Foc: Focal; NR: Not recorded; F/U: Follow-up (months)

muscle-invasive bladder LELC, with all patients remaining free of recurrence after six years of follow-up.^[6]

Selective bladder preservation has been reported to show results

equivalent to immediate cystectomy for TCC, and the SPARE (Selective bladder Preservation Against Radical Excision) trial is currently comparing bladder preservation with radical cystectomy in responders to neoadjuvant chemotherapy.^[7] Our case suggests, in combination with the existing literature, that bladder-preserving therapy may also be used to successfully treat pure/predominant LELC, although we acknowledge the limited follow-up period. Given the favourable prognosis of the pure/predominant forms, coupled with the reported sensitivity to chemotherapy, radical cystectomy may be avoided in these cases.

In conclusion, we present a case that supports the use of systemic treatment, coupled with TUR, to treat pure/predominant LELC. More specifically, it raises the possibility of using a standardised chemotherapy regime, such as that proposed by the SPARE study protocol, as part of a bladder-preserving treatment for LELC.

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