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Lymphoepithelioma-like carcinoma of the urinary bladder: a clinicopathologic study of 13 cases

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Abstract Lymphoepithelioma-like carcinoma (LELCA) of the urinary bladder is a rare variant of bladder cancer characterized by a malignant epithelial component densely infiltrated by lymphoid cells. It is characterized by indistinct cytoplasmic borders and a syncytial growth pattern. These neoplasms deserve recognition and attention, chiefly because they may be responsive to chemotherapy. We report on the clinicopathologic features of 13 cases of LELCA recorded since 1981. The chief complaint in all 13 patients was hematuria. Their ages ranged from 58 years to 82 years. All tumors were muscle invasive. A significant lymphocytic reaction was present in all of these tumors. There were three pure LELCA and six predominant LELCA with a concurrent transitional cell carcinoma (TCC). The remainder four cases had a focal LELCA component admixed with TCC. Immunohistochemistry showed LELCA to be reactive against epithelial membrane antigen and several cytokeratins (CKs; AE1/AE3, AE1, AE3, CK7, and CK8). CK20 and CD44v6 stained focally. The lymphocytic component was composed of a mixture of T and B cells intermingled with some dendritic cells and histiocytes. Latent membrane protein 1 (LMP1) immunostaining and in situ hybridization for Epstein-Barr virus were negative in all 13 cases. DNA ploidy of these tumors gave DNA histograms with diploid peaks (*n*=7) or non-diploid peaks (aneuploid or tetraploid; *n*=6). All patients with pure and 66% with predominant LELCA were alive, while all patients having focal LELCA died of disease. Our data suggest that pure and predominant LELCA of the bladder appear to be morphologically and clinically different from other bladder (undifferentiated and poorly differentiated conventional TCC) carcinomas and should be recognized as separate clinicopathological variants of TCC with heavy lymphocytic reaction relevant in patient management.

Keywords Lymphoepithelioma-like carcinoma · Transitional cell carcinoma · Eptein-Barr virus · Immunohistochemistry · DNA ploidy

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Introduction

Lymphoepithelioma, a tumor originally described within the nasopharynx, is a malignant epithelial neoplasm densely infiltrated by lymphoid cells. It is characterized by indistinct cytoplasmic borders and a syncytial growth pattern [6, 18]. Tumors with a similar histology have been described in the salivary glands, thymus, uterine cervix, skin, lung, stomach, oral cavity, breast, vagina, trachea, and larynx, with rare examples in the renal pelvis and ureter [3, 7]. The term lymphoepithelioma-like carcinoma (LELCA) has been proposed for these histologically unique neoplasms [1]. So far, only 23 cases of LELCA have been reported in the urinary bladder [1, 2, 5, 10, 17, 18]. Distinguishing LELCA and malignant lymphoma [15], or poorly differentiated invasive transitional cell carcinoma (TCC) with an associated inflammatory stromal reaction, is often difficult, but it is imperative because of the reported sensitivity of LELCA to cisplatin-based chemotherapy [5]. This sensitivity led to a successful bladder salvage therapy in patients with

muscle-invasive LELCA of the bladder. Although the tumor histogenesis remains unclear, Young and Eble [16] classified them as undifferentiated carcinoma and considered them to be an aggressive variant of bladder carcinoma with a poor prognosis. However, more recent reports [1, 5] recognized their sensitivity to chemotherapy and a more favorable long-term prognosis than other types of poorly differentiated and undifferentiated invasive carcinomas of the urinary bladder [10, 11], suggesting that LELCA should be classified as poorly differentiated TCC. The Epstein-Barr virus (EBV) has been purported to play an oncogenic role in some of these tumors, because its DNA is present in virtually all nasopharyngeal lymphoepitheliomas, but it is also present in LELCA from the stomach, salivary gland, lung, and thymus [8, 12]. The fact that EBV association with LELCA of the salivary gland and lung is restricted to Asian patients, whereas the association with gastric and thymic LELCA is independent of race [14], is intriguing. To date, all reported cases in the urinary bladder were negative for EBV [10, 12, 14].

We report on the clinicopathological features of 13 examples of LELCA of the urinary bladder recorded since 1981. These cases were investigated for EBV transcripts using in situ hybridization (ISH) and the EBV-encoded latent membrane protein 1 (LMP1). In addition, a large panel of epithelial and lymphoid markers and the adhesion molecule CD44v6 have been immunohistochemically studied in order to determine their utility in defining the histopathology of LELCA and their differential diagnosis. Finally, this study also reports on the DNA ploidy pattern that has not previously been established in LELCA of the urinary bladder.

Materials and methods

Patients

This study included resection specimens from 13 patients. The cases were retrieved from the surgical pathology files of the Reina Sofia University Hospital in a retrospective review of 927 (1.29%) cases of bladder cancer from 1981 to 1998. Clinical information was obtained from patients' records.

Histological and immunohistochemical examination

All specimens were fixed in 10% buffered formalin and embedded in paraffin. Hematoxylin-and-eosin-stained histologic slides from all cases were evaluated and classified according to Amin et al. [1] as pure (100%), predominant (>50%), or focal LELCA (<50%). In predominant and focal LELCA cases, the percentage of the associated tumor component (TCC, adenocarcinoma, squamous cell carcinoma, or carcinoma in situ) was recorded.

For the immunohistochemical study, 4-µm-thick sections were prepared and mounted on coated slides. The sections were deparaffinized in xylene for 10 min and rehydrated in graded alcohol (100%, 96%, and 70%). Immunohistochemical analysis was carried out on selected sections from each case using the streptavidin–biotin peroxidase method. Briefly, sections were incubated overnight with primary antibodies at 4°C. Biotinilated secondary antibodies and the streptavidin–biotin peroxidase complex were applied according to the manufacturer's instructions (LSAB2 kit, Dako, Glostrup, Denmark). Diaminobenzidine was used as a chromogen for visualization (Biomeda Corp., Foster City, Calif.). Endogenous peroxidase activity was blocked by incubating the slides in 1% hydrogen peroxide in methanol for 10 min. For heat epitope retrieval, the slides were treated by boiling in 10 mM citrate buffer (pH 6.0) for 10 min. Appropriate negative and positive controls were used in every experimental procedure. The primary antibodies are listed in Table 1.

In situ hybridization

The presence of EBV in the tumors was tested using ISH for EBV-encoded RNA on sections placed onto 3-aminopropyltriethoxylane-treated slides (Probe-on, Fisher Scientific, Pittsburgh, Pa.), obtained from selected paraffin blocks. The slides were deparaf-

Table 1 Antibodies used and results in lymphoepithelioma-like carcinoma (LELCA) immunophenotyping. *EMA* epithelial membrane artigen; *CK* cytokeratin; *LCA* leukocyte common antigen; *LMP1* latent membrane protein 1

Antibody	Host species	Source	Working dilution	LELCA immunophenotype
EMA	Mouse	Signet (Dedham, Mass.)	Prediluted	+
CK AEl/AE3	Mouse	Signet (Dedham)	Prediluted	+
CK AE1	Mouse	Signet (Dedham)	Prediluted	+
CK AE3	Mouse	Signet (Dedham)	Prediluted	+
CK 7	Mouse	Dako (Glostrup, Denmark)	1:50	+
CK 8	Mouse	Dako (Glostrup)	Prediluted	+
CK 10	Mouse	Dako (Glostrup)	Prediluted	–
CK 18	Mouse	Biogenex (San Ramon, Calif.)	1:200	–
CK 19	Mouse	Dako (Glostrup)	Prediluted	–
CK 20	Mouse	Dako (Glostrup)	1:50	+Focal
LCA	Mouse	Dako (Glostrup)	Prediluted	+Lymphoid cells
CD 45 RO	Mouse	Dako (Glostrup)	Prediluted	+Lymphoid cells
CD 3	Mouse	Dako (Glostrup)	Prediluted	+Lymphoid cells
CD 20	Mouse	Dako (Glostrup)	Prediluted	+Lymphoid cells
CD 68 (PGM1)	Mouse	Dako (Glostrup)	Prediluted	+Histiocytes
Kappa light chain	Rabbit	Dako (Glostrup)	Prediluted	+Lymphoid cells
Lambda light chain	Rabbit	Dako (Glostrup)	Prediluted	+Lymphoid cells
S-100 protein	Rabbit	Dako (Glostrup)	Prediluted	+Dendritic cells
LMP1	Mouse	Dako (Glostrup)	1:50	–
CD44v6	Mouse	Novo Castra (Newcastle, UK)	1:40	+Focal

finized in xylene and a graded alcohol series, digested with proteinase K and dehydrated. Hybridization was performed at 37°C overnight using a biotinylated riboprobe complementary to the EBV early RNAs, EBER1 and EBER2 (Kreatech Diagnostics, Amsterdam, The Netherlands). A positive control from a lymphoepithelioma of nasopharinx known to be strongly positive for EBV and a negative control (the tumor without adding the probe) were used. After several washes, the slides were treated with streptavidin and peroxidase (Biogenex Laboratories, Calif.), followed by 3-amino-9-etylcarbazole as a chromogen.

DNA ploidy

The DNA ploidy of these tumors was investigated using the CAS 200 Image Analysis system on isolated nuclei from formalin-fixed, paraffin-embedded tissue. The isolation of nuclei for image cytometry was performed using the method described by Hedley et al. [9] with a few modifications [4]. Briefly, using the same block from which the tissue sections were obtained, the LELCA and non-LELCA areas were separately dissected from non-tumor tissue using a scalpel blade. Then, three to five 30-µm-thick sections were cut. After acid hydrolysis in 5 N HCl for 60 min at 22°C, the nuclei of the obtained smears were stained according to the Feulgen technique. At least 120 tumor cell nuclei were measured. Before analysis, instrument calibration was achieved using normal rat hepatocytes.

Results

Clinical and pathological data

The main clinical and pathological data from 13 cases of LELCA of the urinary bladder included in this study are presented in Table 2. Of the 13 patients, nine (69%) were men, and the mean age was 73 years (range 58–82 years). Transurethral resection (TUR) was the treatment of choice in all 13 cases, although five (38%) cases additionally underwent cystectomy. Two patients received chemotherapy in addition to TUR.

The pathological stage was tumor (T)2, node (N)0, metastasis (M)0 in nine (70%) cases, T3, N0, M0 in three (23%) cases, and T2, N1, M0 in one (7%) case. Of the 13 cases, three were histologically pure LELCA, six were predominantly LELCA, and the remaining four were focal LELCA. Ten cases of predominant or focal LELCA showed areas of TCC (*n*=8), squamous cell carcinoma (*n*=1), and adenocarcinoma (*n*=1). All cases of LELCA showed an extensive stromal lymphoid inflammatory reaction.

The three patients showing pure LELCA were alive (mean 33 months, range 21–47 months). Of six patients showing predominant LELCA, four (66%) were free of disease, while the remaining two cases were dead (*n*=1) or alive with metastases (*n*=1). All patients (*n*=4) with focal LELCA were dead (mean 17.5 months, range 3–30 months). Five patients had previous (*n*=4) or concomitant cancer (*n*=1) in another organ.

Immunohistochemistry and in situ hybridization

As seen in Table 1, the immunohistochemical study demonstrated positive staining of the epithelial component of

Table 2 Clinicopathologic features and DNA ploidy of 13 cases of lymphoepithelioma-like carcinoma (LELCA) of the urinary bladder. *DOD* died of disease; *NA* not available; *NED* no evidence of disease; *AWM* alive with metastases; *TUR* transurethral resection; *TCC* transitional cell carcinoma;*CA* carcinoma; *ACA* adenocarcinoma; *DOC* died from other causes; *chem* chemotherapy; *SqCC* squamous cell carcinoma; *CT* computed tomography; *HG* high grade

Case no.	Gender/age (years)	Pathological stage		Treatment	Histology of LELCA	Non-LELCA component	Follow-up (months)	LELCA DNA ploidy (DNA index)	Non-LELCA DNA ploidy (DNA index)	Concurrent tumor
		T	N							
1	Male/69	2		TUR	Predominant	HG-TCC	NED (22)	Diploid (1)	Aneuploid (1.4)	Broncogenic CA 13 years earlier
2	Female/69	2	1[a]	TUR+chem	Pure	–	NED (21)	Diploid (0.95)	–	
3	Female/67	2		Cystectomy	Predominant	HG-TCC+CIS	NED (22)	Diploid (1)	NA	
4	Male/73	3		Cystectomy	Predominant	SqCC	NED (37)	Aneuploid (1.3)	NA	Gastric ACA 4 years earlier
5	Male/72	3		Cystectomy	Pure	–	NED (32)	Diploid (1.05)	–	
6	Male/82	2		TUR	Predominant	ACA	NED (49)	Diploid (1.05)	Tetraploid (2.2)	Concomitant prostate ACA
7	Male/74	2		TUR	Predominant	HG-TCC	AWM (25)	Aneuploid (1.5)	NA	Larynx CA+radiotherapy 7 years earlier
8	Male/78	2		TUR	Focal	HG-TCC	DOD (3)	Tetraploid (1.9)	Tetraploid (2)	
9	Female/58	2		Cystectomy	Focal	HG-TCC	DOD (19)	Aneuploid (1.4)	Aneuploid (1.3)	
10	Male/71	2		TUR	Focal	HG-TCC	DOD (30)	Aneuploid (1.4)	Aneuploid (1.5)	Glioblastoma multiforme+radiotherapy 7 years earlier
11	Female/81	2		TUR	Predominant	HG-TCC	DOD (44)	Diploid (0.95)	diploid (0.95)	
12	Male/69	3		Cystectomy	Focal	HG-TCC	DOD (18)	Aneuploid (1.7)	Tetraploid (2)	
13	Male/81	2		TUR+chem	Pure	–	NED (47)	Diploid (1)		

[a] Iliac lymph-node positive using CT scan

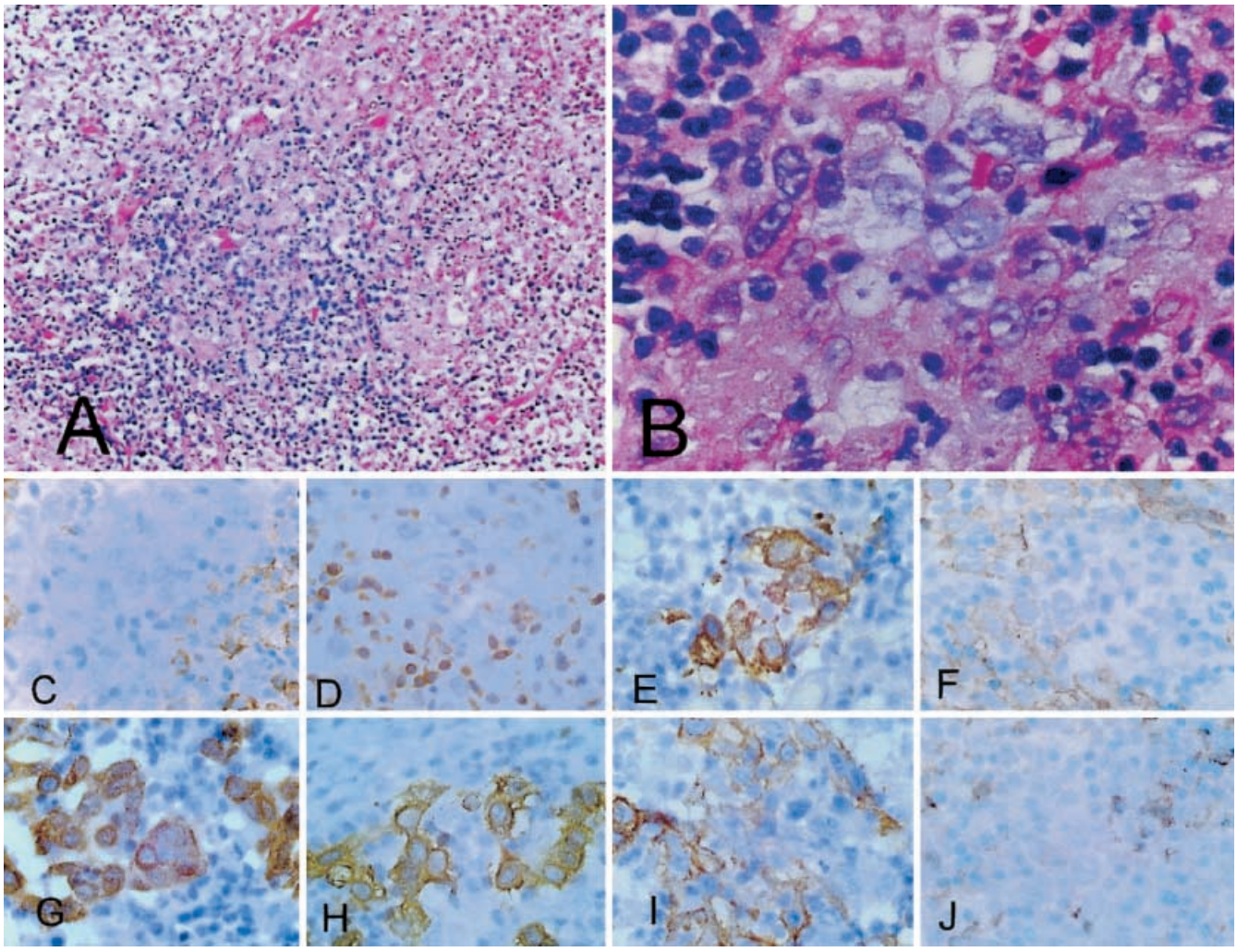

Fig. 1 Lymphoepithelioma-like carcinoma of the urinary bladder. **A** Low power [hematoxylin and eosin (HE), ×100], **B** High power (HE, ×400), **C** CD-20, **D** CD3, **E** CK AE1 **F** CK7, **G** CK8, **H** CK20, **I** CK44v6, and **J** S-100 protein

LELCA with antibodies against epithelial membrane antigen (EMA) and several cytokeratins (CKs; pancytokeratin AE1/AE3, AE1, AE3, CK7, and CK8). CK20 and the adhesion molecule CD 44v6 stained focally but consistently (Fig. 1). Immunostaining against CKs 10, 18, and 19 and LMP1 was negative. Lymphoid markers showed a mixed population of T cells, B cells, and kappa and lambda light chains, intermingled with some S100 protein and CD68 immunoreactive cells. In situ hybridization was negative for the EBV genome in all 13 cases, while the controls gave appropriate results.

DNA ploidy

Image DNA ploidy analysis of nuclear suspension of paraffin-embedded tissues from the 13 cases of LELCA of the bladder gave DNA histograms (Fig. 2) with diploid peaks (n=7) or non-diploid peaks (aneuploid or tetraploid; n=6). The non-LELCA component gave non-diploid peaks in all but one case that was diploid (Table 3).

Discussion

LELCA of the urinary bladder was first reported by Zukerberg et al. [18] as a part of a series of carcinomas simulating lymphoma. In the English literature, 23 cases have been reported so far (Table 3) [1, 2, 5, 10, 16, 18]. Most reported cases of bladder LELCA [10], including the 13 cases reported here that presented with gross hematuria, were solitary and displayed a relatively small size (range 0.9–5 cm). Carcinoma in situ in the adjacent urothelium is seen in 14% of cases. One striking feature of LELCA is its muscular invasiveness. In fact, 19 of 23 previously reported cases [1, 2, 5, 10, 17, 18] and our 13 cases were muscle invasive at the moment of diagnosis.

Most reported cases of LELCA of the urinary bladder had a relatively favorable prognosis when pure or predominant [1, 10, 13]. Only three (13%) of reported cases and two (15%) in our series developed metastases [1, 17]. This is in contrast with small-cell undifferentiated

carcinoma, which presents with metastatic disease at diagnosis in 28% of cases [6, 11]. This favorable prognosis may be related to the host response, expressed as a dense infiltrate composed predominantly of T cells in these tumors, as shown using immunohistochemistry [1, 13] or, perhaps, because the symptoms generated by the inflammatory infiltrate alert patients to seek medical treatment when the tumor is small and still treatable [10]. Indeed, chemosensitivity has been reported as a feature of LELCA. The pure or predominant forms of LELCA have been treated with primary multiagent chemotherapy to try to salvage bladder function [5]. Preliminary results showed no residual disease or metastases between 11 months and 72 months in all of these cases [1, 2, 5], and two in our series, treated with TUR and chemotherapy, were without any evidence of disease. Due to their response to chemotherapy and better prognosis than conventional TCC of the same stage, some authors propose avoidance of radical cystectomy [1, 2]. Our results agree with those of Holmang et al. [10] showing that in contrast to pure or predominant forms, when LELCA is focally present in an otherwise TCC, these patients behave like patients with conventional TCC alone of the same grade and stage. In fact, all four cases that presented focal LELCA in a background of high-grade TCC died of disease 3–30 months from diagnosis.

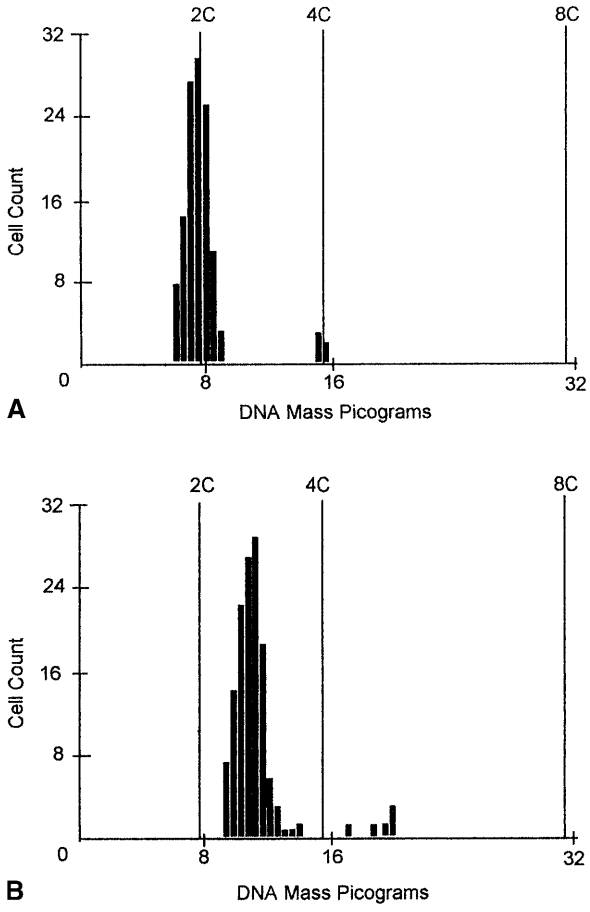

Fig. 2 DNA ploidy histogram in diploid (**A**; DNA index, 0.95) and aneuploid (**B**; DNA index, 1.47) lymphoepithelioma-like carcinoma (LELCA) cases

Table 3 Lymphoepithelioma-like carcinoma (LELCA) of the bladder. Previous studies on 23 cases. *DOD* died of disease; *NA* not available; *NED* no evidence of disease; *TUR* transurethral resection; *TCC* transitional cell carcinoma; *ACA* adenocarcinoma; *DOC* died from other causes

Reference no.	Gender	Age (years)	Pathological stage		Treatment	Histology of LELCA	Non-LELCA component	Follow-up (months[a])
			T	N				
18	Male	76	2	NA	TUR+radiotherapy	Pure	–	NA
5	Male	52	2	NA	TUR+chemotherapy	Pure	–	NED (72)
5	Male	68	2	NA	TUR+chemotherapy	Pure	–	NED (60)
5	Male	63	2	NA	TUR+chemotherapy	Pure	–	NED (11)
17	Male	81	3b	–	Segmental resection+chemotherapy	Pure	–	DOD (41)
1	Female	71	2	–	TUR+chemotherapy	Predominant	TCC	NED (9)
1	Female	67	3b	–	Segmental resection+radiotherapy	Predominant	TCC, ACA	NED (36)
1	Male	55	3	–	Cystectomy	Predominant	TCC	NED (10)
1	Male	71	3	–	Cystectomy	Predominant	TCC	NED (6)
1	Male	79	3b	–	Cystectomy	Predominant	TCC	NED (2)
1	Male	78	3	–	Cystectomy+chemotherapy	Focal	TCC	DOD (84)
1	Male	66	3b	–	Cystectomy	Focal	TCC	DOD (6)
1	Male	68	1	–	Cystectomy	Focal	TCC	Died in Postoperatory
2	Male	72	3b	1	Cystectomy+chemotherapy	Pure	–	NED (29)
10	Female	61	2	NA	TUR+radiotherapy	Pure	–	DOC (18 years)
10	Male	78	1	NA	TUR+radiotherapy	Pure	–	DOC (13)
10	Male	65	2	NA	TUR	Pure	–	NED (24)
10	Female	71	3	NA	TUR+radiotherapy	Predominant	TCC	DOC (21)
10	Female	60	3	–	TUR+radiotherapy+radical cystectomy	Predominant	TCC	NED (104)
10	Female	65	3	–	Partial cystectomy	Predominant	TCC	NED (76)
10	Female	84	1	NA	TUR	Focal	TCC	DOD (66)
10	Male	72	3	–	TUR+radiotherapy+radical cystectomy	Focal	TCC	DOD (68)
10	Male	71	2	NA	TUR+radiotherapy	Focal	TCC	DOD (9)

[a] Unless specified

According to these results, to recognize this unusual variant of bladder cancer seems to be clinically relevant. Hence, an important issue is the differential diagnosis of LELCA. As suggested by Zukerber et al. [18], LELCA of the bladder can be misdiagnosed as malignant lymphoma, which has important therapeutic implications. Another suggested source of error is that when the lymphoid infiltrate is very prominent, the neoplastic cells may be overlooked – assuming them to be reactive histiocytes in origin – and the lesion is then misdiagnosed as chronic cystitis [1, 18]. Besides malignant lymphoma and chronic cystitis, the differential diagnosis of LELCA also includes primary undifferentiated small-cell carcinoma of the bladder, in particular in crushed, inadequately fixed or scant biopsy specimens [1]. Finally, poorly differentiated TCC with a heavy lymphoid stromal infiltrate should be distinguished from LELCA in that the latter is characterized by syncytia of tumor cells, vesicular nuclei, and prominent nucleoli [1]. To rule out such entities, some authors recommend using a wide immunohistochemical panel of CKs and lymphoid markers (B and T cells) [1, 15]. As shown by our results and other reported cases, bladder LELCA are positive for common urothelial markers, including several CKs (AE1/AE3, AE1, AE3, CK7, and CK8). However, LELCA also retains some focal reactivity to CK20 and CD44v6, which might be useful in differential diagnosis with poorly differentiated TCC (positive for both CK20 and CD44v6) and small cell undifferentiated bladder carcinoma (negative for both) [11]. These results may also indicate that LELCA originates from stem cells of the urothelium, whose markers are retained. Given that CD44v6 is positive in TCC and negative in most small cell undifferentiated carcinomas, and CK20 is positive in a subset of bladder TCC, their positivity in LELCA could argue in favor that these tumors should be classified as a distinctive clinicopathological variant of TCC with heavy lymphocytic stromal reaction and relatively good prognosis [10], instead of the previously proposed classification as undifferentiated carcinoma [16]. Another important finding in our paper, not previously reported, is the DNA ploidy pattern, which showed that most surviving patients in our series were DNA diploid. Hence, the DNA ploidy might be an important adjuvant in planning the right therapy in LELCA patients.

First reports invoked a common etiology via EBV infection that may explain the similar histological appearance of the tumor in diverse locations and raises the possibility that patients with bladder LELCA may be at risk for a tumor at another site [5]. In fact, 35% of our cases showed previous or concomitant tumor in another organ. The EBV genome has not been detected in any of the reported bladder cases, including ours [7, 8, 10]. In conclusion, our results and current data suggest that pure and predominant LELCA of the bladder appear to be morphologically and clinically different from other bladder (undifferentiated and poorly differentiated conventional transitional cell) carcinomas and should be recognized as separate clinicopathological variants of bladder TCC, relevant in patient management.

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