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ARTICLE

An expanded immunohistochemical profile of osteoclast-rich undifferentiated carcinoma of the urinary tract

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Abstract

Osteoclast-rich undifferentiated carcinoma of the urinary tract (ORUCUT) is a rare tumor composed of ovoid to spindle-shaped mononuclear cells with intermixed or focally clustered osteoclast-like giant cells. Previous studies have demonstrated that the mononuclear cells are neoplastic cells, while the giant cells are reactive cells of histiocytic lineage. The association between these tumors and classic urothelial carcinomas suggest that the mononuclear cells are derived from urothelial cells; however, no studies have been conducted to assess the immunohistochemical profile of ORUCUT with more specific urothelial markers. This study identified 21 cases of ORUCUT and performed immunohistochemistry for GATA3, uroplakin II, and thrombomodulin along with pancytokeratin (AE1/3) on all cases. Mononuclear cells stained positive in 20 cases (95%) for GATA3 and 19 cases (90%) for thrombomodulin. None of the mononuclear cells were positive for uroplakin II and only three cases showed focal positivity for AE1/3. The osteoclast-like giant cells were negative for GATA3, uroplakin II, thrombomodulin, and AE1/3, providing additional support to a reactive origin for these cells. Additionally, 15 cases (71%) were associated with either in situ or invasive urothelial carcinoma. This study provides an expanded immunohistochemical profile for ORUCUT and more definitively supports a urothelial origin for this tumor.

Introduction

Osteoclast-rich undifferentiated carcinoma of the urinary tract (ORUCUT) is a rare tumor. The histology of ORUCUT is similar in morphology to giant cell tumor of the bone, tendon sheath, and soft tissues and is composed of a population of mononuclear cells with intermixed or focally clustered osteoclast-like giant cells (Fig. 1). Similar histology have been noted in undifferentiated carcinomas from other visceral organs including thyroid, gastrointestinal tract, salivary gland, skin, breast, larynx, lung, and female genital tract [1–9].

The largest immunohistochemical study to date identified six cases of ORUCUT [10] from an earlier work by one of the current authors (JIE). An equal number of tumors arose from the renal pelvis and bladder. In four of six cases, the mononuclear cells showed positive staining for epithelial markers. However, staining was inconsistent between tumors and only one case was reactive for pancytokeratins (Cam5.2 and AE1/3) and CK7. In contrast, the osteoclast-like giant cells stained identically to normal osteoclasts with positivity for CD68, LCA (leukocyte common antigen), CD51, CD54, and negative for cytokeratins and epithelial membrane antigen (EMA). Based on this staining pattern, the giant cells were considered reactive in nature. Tumors behaved in an aggressive manner with four of the six patients deceased within 15 months of diagnosis, mostly due to disseminated disease. This behavior is more akin to a high-grade carcinoma and stands in stark contrast to the more indolent behavior of giant cell tumor of the bone and soft tissue [11–13].

The evidence suggests that the mononuclear cells in ORUCUT represent the neoplastic cells and the association of these tumors with in situ or high-grade papillary urothelial carcinoma in all six cases supported an epithelial origin. In addition, giant cell tumors in other visceral organs, such as the pancreas, have demonstrated robust epithelial staining in the mononuclear cells [14]. To further assess the histopathogenesis of ORUCUT, this study

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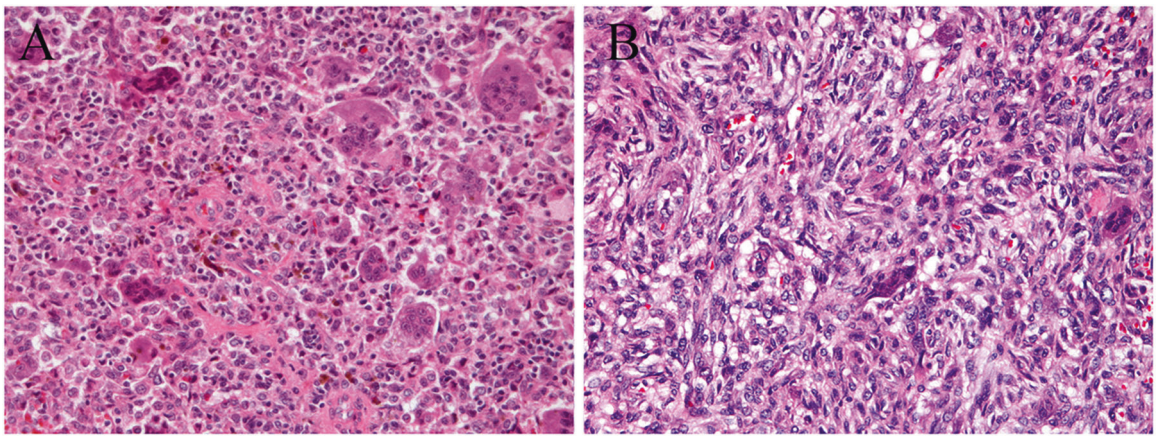

Fig. 1 Typical histology of ORUCUT. **a** Ovoid mononuclear cells intermixed with osteoclast-like giant cells. **b** Occasionally the mononuclear cells exhibited a more spindled morphology

Table 1 Details of antibodies used in immunohistochemistry

Antibody	Clone	Dilution	Vendor
GATA3	L50-823	1:100	Biocare
Uroplakin II	BC21	1:100	Biocare
Thrombomodulin	MS1009	1:100	Dako
Cytokeratin AE1/3	PCK-26	Pre-diluted	Ventana

utilizes the more specific urothelial markers of GATA3, uroplakin II, and thrombomodulin.

Materials and Methods

Historical records, including consultation cases, at two tertiary care hospitals were searched. Seventeen of the twenty-one cases (81%) were from consultation cases from outside institutions received for review by one of the authors (JIE), with the remaining four cases primary to Johns Hopkins Hospital (JHH) and the Hospital of the University of Pennsylvania (HUP). Cases were accessioned between the years 1995 to 2015. None of the 21 cases were previously reported in the literature. Representative hematoxylin and eosin stained and immunohistochemical slides from each case were reviewed by all the authors for agreement on the diagnosis. A single block from each case, which contained both mononuclear cells and osteoclast-like giant cells, was selected for immunohistochemistry from each case for this study. For all cases, the presence of in situ or invasive urothelial carcinoma was also noted.

Immunohistochemistry for all 21 cases was performed at JHH for GATA3, uroplakin II, thrombomodulin, and cytokeratin AE1/3 (Table 1). Immunohistochemistry was performed on 4-μm-thick, deparaffinized sections using the standard streptavidin–biotin–immunoperoxidase complex method. Immunohistochemical results were reviewed by all the authors and were designated as either positive (≥5% of tumor cells staining) or negative (<5% of tumor cells staining). Mononuclear-like and osteoclast-like giant cells were evaluated as separate populations. The percentage of positive tumor cells were quantified and binned as follows: focal (<25%, +), moderate (25–50%, ++), and extensive (>50%, +++).

The research protocol for this study was reviewed at JHH and HUP and approved by their respective Institutional Review Board.

Results

Patient demographics are presented in Table 2. The average age at diagnosis was 73 years (range 55–85) with a male to female ratio of 7:1. The advanced age and male bias is consistent with previous cases in the literature. In 15 (71%) cases the tumor arose in the bladder, with the remaining 6 cases centered in the renal pelvis. All the tumors displayed the classic biphasic morphology of ORUCUT with osteoclast-like giant cells admixed with mononuclear cells (Fig. 1a). Mononuclear cells were often ovoid, but in a few instances appeared spindled (Fig. 1b) In 15 cases (71%) there was association with either in situ or invasive urothelial carcinoma in addition to ORUCUT (Table 2). However, in some cases ORUCUT was adjacent to normal urothelium (Fig. 2).

Immunohistochemistry results are summarized in Table 2. The mononuclear cell population was positive for GATA3 in 95% (20/21) of cases. Sixteen of the twenty (80%) positive cases had moderate to extensive immunoreactivity in the mononuclear cell population (Fig. 3a). Only one case did not stain for GATA3. Thrombomodulin staining in the mononuclear cells was seen in 90% (19/21) of cases. In contrast to GATA3 staining, thrombomodulin

Table 2 Demographic information and immunohistochemical profiles of 21 cases of ORUCUT

Case	Age (years)	Sex	GATA3	Thrombomodulin	AE1/3	Uroplakin	Tumor site	Associated lesions
1	82	Male	+++	+	Negative	Negative	Renal pelvis	INUC
2	77	Male	+++	+	Negative	Negative	Bladder	None
3	79	Male	+++	+	Negative	Negative	Bladder	None
4	73	Male	+++	+	Negative	Negative	Renal pelvis	INVPAP
5	55	Male	++	+	Negative	Negative	Bladder	CIS
6	74	Male	+++	+	Negative	Negative	Bladder	INUC, CIS
7	68	Male	+	Negative	Negative	Negative	Bladder	None
8	63	Female	+	+	Negative	Negative	Renal pelvis	CIS
9	84	Male	+++	++	++	Negative	Bladder	INUC, CIS
10	76	Male	+++	+	Negative	Negative	Bladder	None
11	73	Female	+++	Negative	+	Negative	Renal pelvis	INUC
12	76	Male	++	+	+	Negative	Bladder	INUC
13	66	Male	++	+	Negative	Negative	Bladder	CIS
14	84	Male	+++	+	Negative	Negative	Bladder	None
15	72	Male	Negative	+	Negative	Negative	Bladder	INUC, INSQ
16	73	Male	++	+	Negative	Negative	Bladder	None
17	85	Male	+++	+	Negative	Negative	Renal pelvis	CIS
18	76	Female	++	+	Negative	Negative	Bladder	LGPAP
19	63	Male	+++	+	Negative	Negative	Bladder	INVPAP
20	64	Male	+++	+	Negative	Negative	Bladder	HGPAP
21	73	Female	+	+	Negative	Negative	Kidney	CIS

INUC invasive urothelial carcinoma, *PAPUC* papillary urothelial carcinoma, *CIS* carcinoma in situ, *INVPAP* invasive high-grade papillary urothelial carcinoma, *INSQ* invasive squamous cell carcinoma, *LGPAP* low-grade papillary urothelial carcinoma, *HGPAP* high-grade papillary urothelial carcinoma

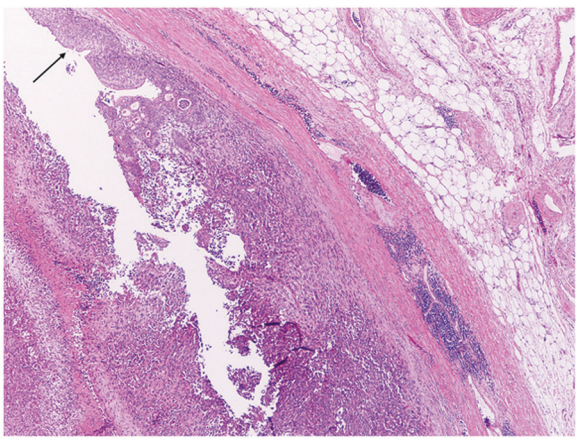

Fig. 2 ORUCUT arising adjacent to normal urothelium (arrow)

staining was focal in all cases, except for one that had moderate immunoreactivity (Fig. 3b). The case which was negative for GATA3 in the mononuclear cells was positive for thrombomodulin. Fourteen percent of cases (3/21) were positive for AE1/3 in the mononuclear cells. In all instances, this occurred in the tumor closest to in situ or invasive urothelial carcinoma. In none of the cases did the mononuclear population stain positive for uroplakin II. The osteoclast-like giant cells in all cases were negative for GATA3, thrombomodulin, uroplakin, and AE1/3.

Discussion

ORUCUT has been rarely described in the literature with approximately 20 case reports and small case series reported to date [15–33]. The largest prior case series by one of the current authors (JIE) on only six cases concluded that the mononuclear cells in ORUCUT were derived from urothelium based on three main findings: (1) the presence of at least focal epithelial staining (either AE1/3, Cam5.2, CK7 and or EMA) in 4/6 cases; (2) association of in situ or high-grade papillary urothelial carcinoma in all six cases; and (3)

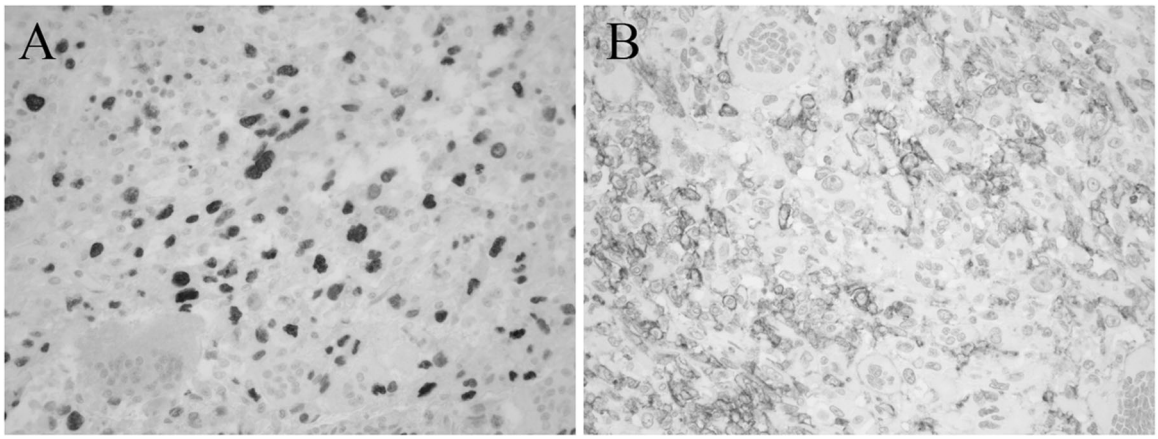

Fig. 3 Immunohistochemical staining in ORUCUT. **a** GATA3 showed extensive nuclear staining in most cases. **b** Thrombomodulin staining tended to be patchy compared to GATA3. Osteoclast-like giant cells were negative for both stains

matched p53 positivity in the conventional urothelial carcinoma and the ORUCUT mononuclear cells [10]. Overall in the literature, 22/28 (79%) of cases of ORUCUT report associated conventional urothelial carcinoma. Further, the presence of mitotic activity and nuclear pleomorphism in the mononuclear cells highlighted their malignant behavior [10]. The lack of atypia and consistent immunohistochemical staining of the osteoclast-like giant cells supports their non-neoplastic, reactive, and histiocytic origin. The current study focused on further classifying the mononuclear cell population with more specific urothelial markers.

GATA3 belongs to a family of zinc-finger transcription factors. A systematic study of 2,500 epithelial and non-epithelial tumors for GATA3 reported >90% staining in urothelial, ductal and lobular breast carcinomas, cutaneous basal cell carcinomas, and trophoblastic and endodermal sinus tumors. In addition, positivity was common in squamous cell tumors, skin adnexal tumors, mesothelioma, salivary gland, and pancreatic ductal carcinomas. Mesenchymal tumors displayed only sporadic positivity [34]. Thus, GATA3 is a sensitive and a specific maker for urothelial neoplasms when evaluating primary tumors in the bladder and renal pelvis [34, 35]. We observed positive staining in 95% of cases, which is strong evidence that the mononuclear cells are derived from urothelium.

Thrombomodulin is an integral membrane protein expressed on the surface of endothelial cells to serve as a cofactor for thrombin. Expression of thrombomodulin has also been noted in many tumors including urothelial, squamous, endothelial vascular tumors, and some adenocarcinomas. It is a fairly sensitive stain for urothelial carcinoma showing positivity in approximately 70–90% of cases [36, 37]. In this series, thrombomodulin expression was seen in 90% of cases. In contrast to GATA3, the staining was patchy in all cases, except one. Positive staining for thrombomodulin further supports a urothelial origin for ORUCUT.

Uroplakin is a transmembrane protein found in normal and neoplastic urothelium. Various antibodies have been formulated against this target. Uroplakin II has the highest sensitivity in this group reported between 44 and 80%, but overall has lower sensitivity for urothelial carcinoma than GATA3 and thrombomodulin [38, 39]. Uroplakin II was negative in all 21 cases. This is not surprising given the lower sensitivity of the antibody and the undifferentiated nature of ORUCUT. Staining with AE1/3 was predominantly negative, except for focal staining in three cases. Previously, multiple keratins were required to establish positive results in most cases [10].

Osteoclast-like giant cells were negative for GATA3, thrombomodulin, uroplakin II, and AE1/3, once again demonstrating their non-epithelial derivation. Like previous reports the osteoclast-like giant cells lacked atypia or mitosis, supporting their reactive and non-neoplastic nature.

Overall, the findings of this study more definitively support a urothelial origin for ORUCUT with positivity for two of three sensitive and specific markers of urothelial differentiation in the vast majority of cases. Although not all cases had concurrent conventional urothelial carcinoma, the majority showed this association further supporting that ORCUT is an undifferentiated variant of urothelial carcinoma.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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