Osteoclast-Rich Undifferentiated Carcinoma of Renal Pelvis: Case Report

Renal Pelvisin Osteoklasttan Zengin İndiferansiye Karsinomu

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Geliş Tarihi/*Received:* 11.01.2013
Kabul Tarihi/*Accepted:* 31.05.2013

Previously presented as a poster at the 21st National Congress of Pathology, November 7-11, Izmir, Turkey.

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ABSTRACT Tumors with osteoclast-like giant cells have been reported in many organs such as pancreas, liver, lung, thyroid gland but they are rarely seen in the renal pelvis. To our knowledge, 12 patients were reported to date and in 9 cases accompanying in situ/invasive urothelial carcinoma component was present. Tumors containing both malignant epithelial and malignant mononuclear stromal component with reactive, osteoclast like giant cells is a rare entity in urinary tract. There seems to be a mesenchymal-epithelial interaction in the histogenesis. However, it is uncertain whether epithelial-to-mesenchymal differentiation occurs or separate cell clones constitute the tumor. Further investigation is needed to explore the etiology, histogenesis and biological behaviour of this neoplasm. Here, we present the case of a 81-year old female patient who presented with hematuria, flank pain and nausea, and showing histological features of this neoplasm.

Key Words: Osteoclasts; giant cell tumors; carcinoma; kidney pelvis

ÖZET Osteoklast benzeri dev hücre içeren tümörler pankreas, karaciğer, tiroid bezi gibi pek çok organda görülebilmektedir fakat renal pelviste nadir karşımıza çıkarlar. Mevcut verilere göre, bugüne kadar 12 olgu bildirilmiştir ve 9 olguda in situ/invaziv ürotelyal karsinom alanları bulunmaktadır. Önceki çalışmalarda bu tümörlerin in situ/invaziv ürotelyal karsinomla ilişkili oldukları öne sürülmüş olmasına karşın histogenez halen tartışmalıdır ve prognozu kötüdür. Bu makalede hematüri, yan ağrısı ve bulantı ile başvuran ve bu tümörün histomorfolojik özelliklerini sergileyen 81 yaşında kadın hasta sunulmaktadır. Hem malign epitelyal hem de malign stromal bileşenlere sahip osteoklast benzeri dev hücreli tümörler üriner traktusta çok nadirdir. Histogenezde mezenkimal-epitelyal etkileşimin rolü olması muhtemeldir ancak bu tümörlerin etyolojisinin, histogenezinin ve biyolojik davranışının aydınlatılabilmesi için daha ayrıntılı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Osteoklastlar; dev hücreli tümörler; karsinom; renal pelvis

Turkiye Klinikleri J Case Rep 2013;21(3):120-4

Tumors with osteoclast like giant cells are rarely seen in the renal pelvis. They were first described by Kimura et al in 1983.[1] In 2006, in a study of six patients, Baydar et al suggested that these tumors were associated with urothelial carcinoma and used the term "osteoclast rich undifferentiated urothelial carcinoma".[2] To our knowledge, 12 patients were reported to date, their age differed between 55-81, 7 out of 12 were male and most importantly, accompanying in situ/invasive urothelial carcinoma component was present in 9 patients.[1-6] Osteoclast-like giant cell tumors containing both malignant epithelial and malignant mononuclear

stromal component were reported in many organs such as lung, pancreas, liver and thyroid gland as well as urinary tract.[7-10] Here, we present the case of a 81-year old female patient showing histological features of "osteoclast-rich urothelial carcinoma" who died four months after the surgery.

CASE REPORT

A 81-year-old female was admitted to Ege University Faculty of Medicine Hospital with hematuria, flank pain and nausea. She had a history of diabetes mellitus type II and long term hypertension. In addition, she had cardiac by-pass 12 years ago and had surgery for kidney stone in her left kidney twenty-five years ago. Physical examination showed no significant finding. Magnetic resonance imaging (MRI) revealed a 3x2 cm mass in her right renal pelvis and the patient underwent a radical right nephroureterectomy. No metastatic lesions were found on the MRI. The patient who did not receive adjuvant chemotherapy and follow up later died four months after the surgery. Although no autopsy was performed and no evidence for metastatic disease were found on the initial MRI, distant metastasis is suspected.

PATHOLOGICAL FINDINGS

Grossly, there was a 4x3,5 cm white mass located in the renal pelvis (Figure 1A). Microscopically, the tumor was composed of a papillary urothelial carcinoma and accompanying component which was consisted of mononuclear cells and multinucleated giant cells. The mononuclear cells had oval nuclei with prominent nucleoli and vesicular chromatin. Nuclear pleomorphism was noted and in some areas these cells showed spindled morphology. The average number of mitoses was 27 per ten high power fields, the presence of atypical mitoses was

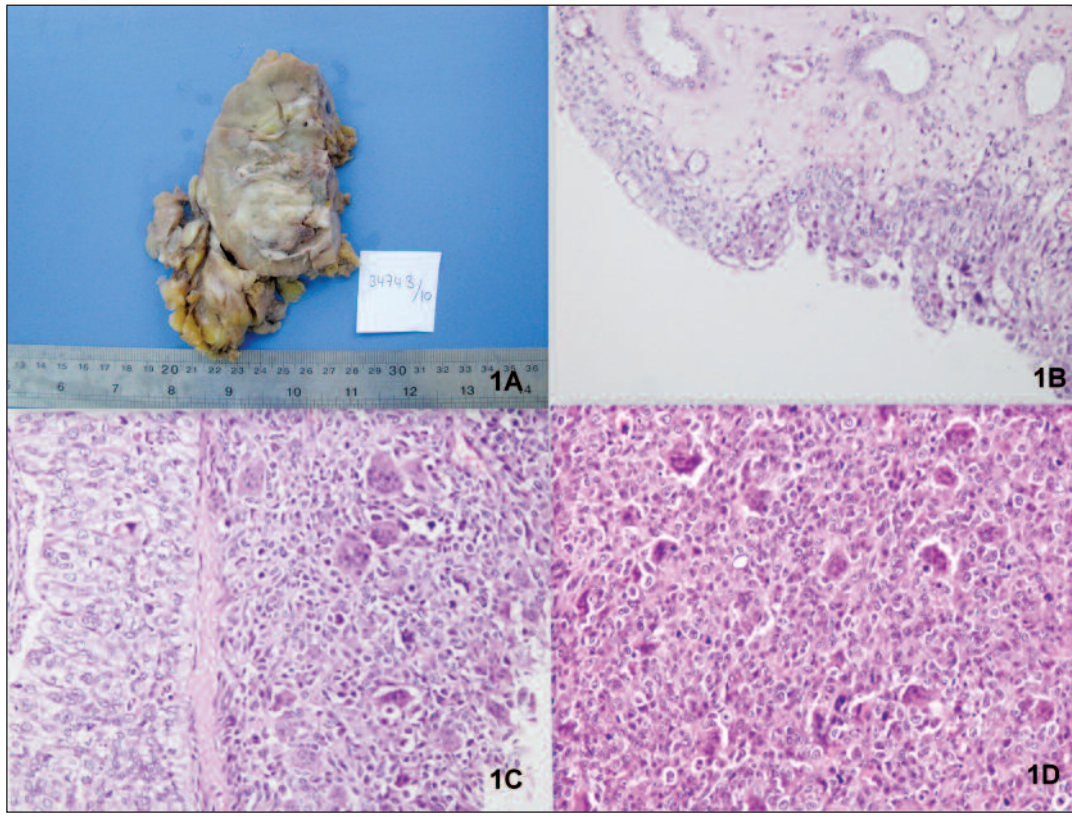

FIGURE 1: A) Gross picture of 4x3cm mass located in renal pelvis after 10% buffered formaline fixation, **B)** Urothelial carcinoma in situ areas in renal pelvis (x20), **C)** Urothelial carcinoma adjacent to undifferentiated component (x20), **D)** Multinucleated giant cells were dispersed between mononuclear cells and the presence of atypical mitoses was remarkable (x20).

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remarkable (Figure 1D) and large areas of necrosis were present. The multinucleated giant cells were similar to osteoclastic giant cells. They had 10 to 30 nuclei with eosinophilic cytoplasm. No mitoses or cytological atypia were noted in the giant cells. The urothelial component included both high grade carcinoma and carcinoma in situ areas (Figure 1B, C). Renal parenchyma invasion was seen and also urothelial displasia and carcinoma in situ areas were observed in ureter and bladder cuff samples. No evidence of osseous or cartilaginous differentiation was seen.

Immunohistochemically; pan-cytokeratin (AE-1/AE-3), cytokeratin 7, high molecule weight cytokeratin (Figure 2C, D), cytokeratin 19, epithelial membrane antigen (EMA) and p63 were positive in urothelial carcinoma cells and both mononuclear and giant cells were not reactive for these immunohistochemical markers. Mononuclear cells and giant cells were vimentin immunoreactive (Figure 2B). Focal staining with S100 in mononuclear cells was seen. Giant cells were positive for CD68 (Figure 2A) and weak staining for smooth muscle actin (SMA) was noted in the cytoplasm of the giant cells. Cytokeratin 20, desmin and ß-HCG were negative in both areas. Both urothelial neoplastic cells and mononuclear cells expressed p53. Ki-67 (MIB 1) was also positive in great majority of p53-positive cells. On the contrary, osteoclast-like giant cells were negative for p53 and Ki-67. Immunohistochemical findings are summarized in Table 1.

DISCUSSION

Osteoclast-like giant cell tumors of urinary tract are thought to be associated with conventional urothelial carcinoma. Histologically, these tumors are composed of ovoid mononuclear cells, reactive osteoclast like giant cells and papillary urothelial car-

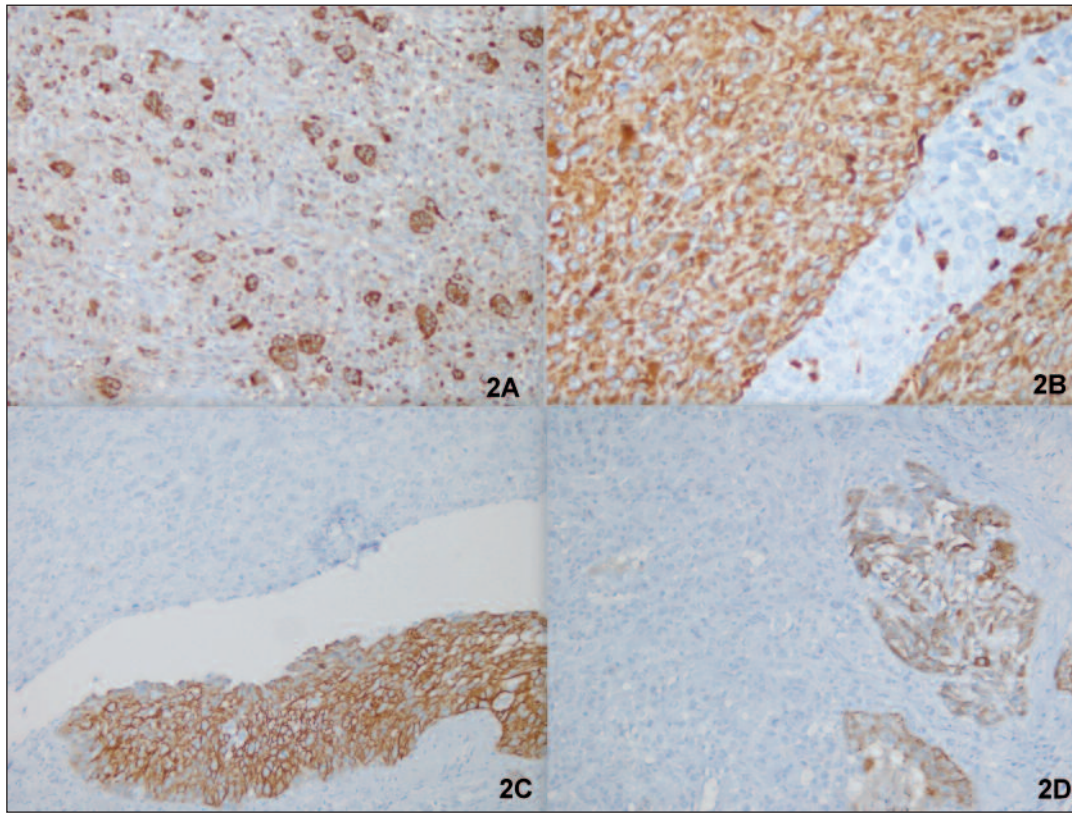

FIGURE 2: A) CD68 positivity in mononuclear cells and osteoclastic giant cells (x20), **B)** Undifferentiated component was stained positive for vimentin (x20), **C)** In situ urothelial carcinoma cells showing cytokeratin 7 positivity, adjacent to the undifferentiated component (x20), **D)** A group of urothelial carcinoma cells trapped in mononuclear component and showing high molecule weight cytokeratin positivity (x20).
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TABLE 1: Immunohistochemical findings.

	Urothelial carcinoma cells	Mononuclear cells	Giant cells
Pancytokeratin (AE-1/AE-3)	+	-	-
Cytokeratin 7	+	-	-
HMW			
Cytokeratin	+	-	-
Cytokeratin-19	+	-	-
Cytokeratin 20	-	-	-
EMA	+	-	-
P63	+	-	-
Vimentin	-	+	+
CD68	-	+	+
SMA	-	-	+
Desmin	-	-	-
S100	-	Focal staining	-
B-HCG	-	-	-
P53	+	+	-
Ki67	+	+	-

HMW-Cytokeratin: high molecule weight cytokeratin; EMA: epithelial membrane antigen; SMA: smooth muscle actin; ß-HCG: human chorionic gonadotropin.

cinoma areas. Atypical mitoses and/or large areas of necrosis may be present. Mononuclear cells show nuclear pleomorphism and in some cases, spindled morphology. Accompanying urothelial neoplasm exhibits histological features between in situ to high grade carcinoma. Immunohistochemically; urothelial neoplastic cells are stained positive for pancytokeratin (AE-1/AE-3), cytokeratin 7, cytokeratin 19, high molecule weight cytokeratin, p63, and EMA. Multinucleated giant cells are of histiocytic origin and stained positive for CD68. Also, they are negative for cytokeratins and EMA, supporting that they are not of epithelial origin.

Three entities should be considered in differential diagnosis particularly: sarcomatoid variant of urothelial carcinoma, urothelial carcinoma with giant cells and urothelial carcinoma with trophoblastic differentiation. According to WHO classification, the term "sarcomatoid variant of urothelial carcinoma" is used for biphasic malignant tumors which is composed of both undifferentiated epithelial cells and mesenchymally-derived spindle cells.[11] Reactive giant cells may be present but this neoplasm is consisted of predominantly spindle cells and also a myxoid stroma, osseous or cartilaginous differentiation may be seen. In urothelial carcinoma with giant cells, giant cells are of epithelial origin, malignant and positive for cytokeratins. The giant cells are also malignant in urothelial carcinoma with trophoblastic differentiation and they express human chorionic gonadotropin (ß-HCG).

In our case, giant cells and mononuclear cells were stained positive for vimentin. It is accepted that formation of osteoclast-like giant cells seen in this neoplasm is the result of a reactive process. On the other hand, there is a likelihood that mononuclear cells are either of mesenchymal origin or they underwent epithelial-to-mesenchymal differentiation. In some of the previous reports, mononuclear cells were reported to be stained positive for cytokeratins and the presence of desmosomes and cytokeratin filaments in these cells had been demonstrated on electron microscope.[3] Although this finding may suggest that mononuclear cells are of epithelial origin, that does not explain when epithelial to mesenchymal differentiation occurs. There could be two possible explanations addressing this situation: 1) mononuclear cells are of epithelial origin and they differentiate into

mesenchymal cells at some point of tumor growth and differentiation, 2) two separate (i.e. both epithelial and mesenchymal) pathways are triggered and both cell clones constitute this tumor, suggesting that mononuclear cells are of mesenchymal origin and they differentiate into epithelial cells at some point of tumor growth and differentiation. Further investigation is needed to explore these mechanisms.

Both urothelial neoplastic cells and mononuclear cells expressed p53. This finding suggests that there may be a common carcinogenesis pathway in both urothelial cells and mononuclear cells. Ki67 was also positive in great majority of p53-positive cells. Also, the average number of mitoses was 27 per ten high power fields and atypical mitoses were present in mononuclear component. Therefore, it is clear that these cells are malignant and show an aggressive behaviour.

In a study of six patients with osteoclast-like giant tumor in urinary tract, Baydar et al. described this neoplasm as "osteoclast-rich undifferentiated urothelial carcinoma".[2] Although it seems to be the best description so far, we believe that the term "undifferentiated" does not quite reflect the histogenesis. If it is considered that mononuclear cells and carcinoma cells share the same origin, the term "poor differentiated" could be used instead of the term "undifferentiated", but even in this case it would not emphasize the possible mesenchymal differentiation and/or biphasic nature. Since similar tumors were reported in many organs such as pancreas, liver, thyroid gland as well as urinary tract, a common terminology may be used for this type of tumor. As more data on the etiology and histogenesis is explored, changes in terminology will be inevitable.

In conclusion, osteoclast-like giant cell neoplasms of the urinary tract are rare. Osteoclast-like giant cell tumor containing both malignant epithelial and malignant mononuclear stromal component is a rare entity in the renal pelvis. On the other hand, osteoclast-like giant cells seen in the osteoclast-rich urothelial carcinoma of renal pelvis are resulted from a reactive process. There seems to be a mesenchymal-epithelial interaction in the histogenesis. However, it is uncertain whether epithelial-to-mesenchymal differentiation occurs or separate cell clones constitute this tumor. Further investigation is needed to explore the etiology, histogenesis and biological behaviour of this neoplasm.

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