Osteoclast-like Giant Cell Urothelial Carcinoma of Urinary Bladder – Case Report and Differential Diagnosis Considerations

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\section*{Abstract}

\textbf{Introduction and Objectives.} Osteoclast-like giant cell urothelial carcinoma is a rare type of urinary bladder tumor and is represented by a biphasic malignant neoplastic proliferation of mononuclear cells and osteoclast giant cells-like. It is characterized by high stage at diagnosis, high clinical aggressiveness and poor prognosis.

\textbf{Materials and Methods.} We present the case of a 56 years old smoker male patient, who came to emergency with gross hematuria and underwent bladder transurethral resection.

\textbf{Results.} Histopathological examination was suggestive for a high-grade infiltrating urothelial carcinoma with osteoclast-like giant cells.

\textbf{Conclusions.} Immunohistochemical tests supported the diagnosis of osteoclast like giant cell urothelial carcinoma of bladder. The presence of osteoclast-giant cells implies various considerations of differential diagnosis with malignant but also benign lesions.

\textbf{Keywords:} bladder, urothelial carcinoma, osteoclast-like giant cell, immunohistochemistry
Introduction
Most malignancies of the bladder urothelial carcinoma are urothelial carcinomas, according to 2004 World Health Organization [1].

Osteoclast-like giant cell urothelial carcinoma, also called osteoclast-rich undifferentiated urothelial carcinoma with extrasosseous location are rare, especially in the bladder [2].

The presence of giant cells reactive stromal component level in urothelial carcinoma has been reported and it was found that in most cases they mask urothelial proliferation. For this reason, this entity is a problem of differential diagnosis with other lesions containing giant cells. [3,4,5,6,7,8].

Materials and methods
We present the case of a 56-years-old smoker male patient, falling in the specific age group that manifests malignant neoplasia of the bladder.

He complained of gross hematuria and dysuria. There was no history of bladder cancer in patient’s family. Cystoscopical examination revealed apedunculated tumor lesion of 3/2/2 cm, covered with hematic clots, located on the right posterolateral wall. The material excised by transurethral bladder resection surgery in the Department of Urology of Saint Andrew County Emergency Hospital of Constanta has identified a high-grade infiltrative urothelial carcinoma with osteoclast-like giant cells. The histopathological and immunohistochemical techniques were performed in the Clinical Service of Pathology of the same hospital. The specimen was fixed in 10% formalin and included in five blocks. The sections were stained with Hematoxylin-Eosin, van Gieson and monoclonal antibodies were applied. Antibody panel is represented by:
- Monoclonal Mouse Anti-Human CK7, Clone OV-TL 12/30 Isotype IgG1, kappa;
- Monoclonal Mouse Anti-Human CK20, Clone Ks20.8 Isotype IgG2a, kappa;
- Monoclonal Mouse Anti-Human CD68, Clone KP1 Isotype IgG1, kappa;
- Monoclonal Mouse Anti-Human Vimentin, Clone V9 Isotype IgG1, kappa;
- Monoclonal Mouse Anti-Human Cytokeratin, High Molecular Weight (HMWCK), Clone 34βE12 Isotype IgG1, kappa;
- Monoclonal Mouse Anti-Human Desmin, Clone D33 Isotype IgG1, kappa;
- Monoclonal Mouse Anti-Human CD34, Class II Clone QBEnd 10 Isotype IgG1, kappa;
- Monoclonal Mouse Anti-Human Ki67, clone MIB-1;
- Monoclonal Mouse Anti-Human prostatic antigen (PSA), Clone ER-PR8 Isotype IgG1, kappa.

The immunohistochemical techniques were performed according to the manufacturer’s recommendations.

Microscopic images were taken with a Nikon Camera using a Nikon Eclipse E600 Microscope.

Results
Macroscopic examination revealed the presence of multiple fragments with variable diameters, which measures overall 8/4,5/1 cm, weighting 30 grams, gray colored with hemorrhagic and green areas, low consistency.

Histopathological examination revealed undifferentiated malignant neoplastic proliferation of large cells with epithelioid appearance, which associates multinucleated giant cells with solid or alveolar architecture, in some areas lined by urothelium with marked atypia. Histopathological characters are suggestive for diagnosis of infiltrative high grade urothelial carcinoma with osteoclast-like giant cells (Fig. 1), with necrosis and hemorrhage associated. The immunohistochemical methods were mandatory to confirm the histopathological entity, in order to realize a differential diagnosis with neoplasms of muscle origin.

Fig. 1. Osteoclast-like giant cells in high grade urothelial carcinoma (HE stain, 100x)

The immunoprofile was as follows:
- CK7 and CK20 diffusely positive in malignant cells;
- Vimentin diffusely positive in tumor cells (Fig. 2);
Clinical cases

- CD68 positive in giant cells (Fig. 3).
- HMWCK, clone 34βE12, positive in atypical urothelial cells, negative in malignant cells;
- Desmin negative in malignant cell proliferation;
- CD34 negative in malignant cells;
- Ki67 positive in 30-35% of malignant cell population (Fig. 4);
- PSA negative in neoplastic cells.

Immunohistochemical tests (CK positive, Vimentin positive in mononuclear cells and CD68 positive in giant cells), correlated with histopathological aspects supports the histopathological diagnosis of osteoclast-like giant cell urothelial carcinoma or osteoclast-rich undifferentiated urothelial carcinoma.

Discussions

Osteoclast-rich undifferentiated carcinoma is a type of urothelial carcinoma which represents a proliferation of malignant epithelial cells accompanied by mononuclear osteoclast-like giant cells. There are identified areas of tumor cells identical to bone tumors. It is considered that giant cells are of histiocytic origin, with histopathological and immunohistochemical features similar to osteoclasts, lacking mitotic activity. Giant cells are positive to CD68 or CD45 and are negative to epithelial markers, while mononuclear cell component express Vimentine, EMA and cytokeratin [5,9,10].

Immunohistochemical exam supports epithelial origin of mononuclear cells and reactive or histiocytic origin of giant cells. Genetically, have been found origin of osteoclast-like giant cells in the ductal epithelium based on K-ras mutation oncogene [11]. A giant cell formation theory refers to the fusion of macrophages, which shows an affinity to the primary tumor due to the secretion of various factors released by cells component [12].

Osteoclasts giant-cell presence in extraosseus lesions appears in sarcomatoid carcinomas, pleomorphic giant-cell carcinomas, invasive urothelial carcinoma with trophoblast differentiation, urothelial carcinoma with giant cells reactive stromal process (pseudosarcomatous myofibroblastic proliferations), lesions with the classical morphology of osteoclastic giant-cell tumors, inflammatory myofibroblastic tumor, and sarcomas, especially leiomyosarcomas [13, 14, 15,16]. We will detail below the elements on which it is performed histopathological differential diagnosis of osteoclast-rich undifferentiated carcinoma of the others injuries listed.

Sarcomatoid variant of invasive urothelial carcinoma is a malignant neoplastic proliferation consisting of epithelial and mesenchymal compound, characterized by distinct histopathologic and immunohistochemical profile. Immunohistochemical exam shows that epithelial component is positive at least focal to epithelial markers, which differentiate it from pure sarcomas, while mesenchymal contingent reacts to vimentin...
Nomenclature of this histopathological entity is controversial. In some studies, sarcomatoid carcinoma is synonymous with carcinosarcoma, while others are different lesions, although differentiation criteria are difficult to apply [19,20]. Carcinosarcoma term refers to a tumor of epithelial origin accompanied by sarcomatous aspects, with the presence or absence of heterologous elements [21].

It is considered that sarcomatoid carcinoma is an entity that represents a separate histopathological malignant neoplastic cell proliferation with spindle cells, whose epithelial differentiation requires immunohistochemical evaluation. Immunohistochemical examination shows positivity of malignant epithelial cells to cytokeratin, whereas stromal elements are characterized by immunostaining to vimentin [22,23,24].

In terms of cytology aspects of malignant neoplastic cells, Arita et al. postulated that they are not completely aware of that and until now it was performed one analysis of this type. According to the study, tumor cells of sarcomatoid urothelial carcinoma are large, with irregular edges, large, round-oval nuclei, with nucleoli identified occasionally associated with necrotic lesions and rare atypia in spindle cells [25,26].

Invasive urothelial carcinoma with trophoblastic differentiation is a variant of urothelial carcinoma, not a germ cell tumor, that associates high levels of human chorionic gonadotrophin (HCG) in serum of 10-30% patients diagnosed with bladder cancer [27]. Variant of urothelial carcinoma contained giant cells is positive for human chorionic gonadotrophin, alkenal placental phosphatase, placental lactogen [28].

Urothelial carcinoma with giant cells reactive stromal process is characterized by the presence of atypical mesenchymal cells in stroma, without mitotic activity in either primary or secondary tumors. The immunohistochemical epithelial markers are negative in the stromal cells [29,30,31].

Giant cell carcinoma, a form of poorly differentiated urothelial carcinoma is characterized microscopically by a high degree of nuclear atypia, multiple nuclei, a variable number of nucleoli or macronucleoli, abundant cytoplasm and large cells of hystiocitic origin. In this case, the giant cells are cytokeratin negative and positive for vimentin [21,32,33].

Pseudosarcomatous myofibroblastic proliferations are characterized by immunohistochemical positivity to pancytokeratine, smooth muscle actin, desmin, Alk-1 protein, while sarcomatoid carcinoma is positive, in addition, to high-molecular-weight cytokeratin and p63 [34]. Inflammatory myofibroblastic tumor is a pseudosarcomatous lesion represented by a proliferation of spindle cells and myoepithelial lymphocytic inflammatory infiltrate with positive expression to SMA, EMA and negative Desmin [35].

Leiomyosarcomas is the most common malignant tumor nonepithelial bladder. Microscopic can be observed by a proliferation of spindled cells with eosinophilic fascicles of cytoplasm, cytoplasmic vacuoles and blunt ended nuclei with variable atypia, infiltrative margins which invades muscularis propria [36]. Immunohistochemical cell proliferation express Desmin, Actin and is negative to high-molecular-weight cytoketatin and p63 [37,38].

Conclusions

The accurate diagnosis of these rare histopathological type of tumor is very important due to its resemblance to other giant cell-rich lesions, mainly because of differential diagnostic considerations that are implied, as well as prognostic and therapeutic implications. Immunohistochemical examination proved once more certainty usefulness in the diagnosis of this malignant neoplasm.

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