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THE HISTOLOGICAL AND IMMUNOHISTOCHEMICAL APPEARANCE OF A VERY RARE ENTITY – BELLINI'S COLLECTING DUCT CARCINOMA

A.C. TINCA[1] M.C. ȘINCU[1*] D.H. PORAV[2]

Abstract: *The collecting Bellini's duct carcinoma is a very rare neoplasm that has the origin in the distal segment of the renal ducts. We present the case of a 64 female patient who underwent nephrectomy for a right renal mass. On the usual stain, the mass presented a tubular and solid architecture, with high pleomorfism. The diagnosis of collecting carcinoma was established with the help of immunohistochemistry. There are few cases described in the literature, most of them highlighting the difficulty in establishing the origin of this lesion, the variable immunohistochemical expression of the tumor and the high risk of metastasis and mortality.*

Key words: *Bellini, immunohistochemistry, rare neoplasia.*

1. Introduction

The Bellini carcinoma, also known as the collecting duct carcinoma (CDC), is a very rare entity with origins in the renal medulla, in the distal segment of the ducts. This tumor has a percent of appearance below 2% (some authors believe that below 1%) of all the neoplasms with renal origin. CDC has a poor prognosis and it is, according to some studies, the most aggressive tumoral lesion of the kidney. The median age of appearance is around 62 years old and male patients are more often affected, with a ratio of 2:1 compared to female patients.

The first author who described this lesion briefly was Mason, back in 1955. The one who developed the description and added more details, such as mentioning the origins in the epithelia of the ducts is Jimenez, in 1976, while Fleming and Lewi, later in 1986, defined the criteria for the complete diagnosis [4, 5], [7].

[1] Clinical County Hospital Mureș
[2] University of Medicine, Pharmacy, Sciences and Technology, Târgu Mureș
*corresponding author: mihaela.sincu02@gmail.com

According to ISUP (International Society of Urological Pathology), Bellini carcinoma diagnosis should be established in lesions which have predominantly a tubular architecture, stromal reaction such as desmoplasia and cells with high pleomorphism which do not resemble any other tumor from the renal cell carcinoma or urothelial carcinoma spectrum [8], [13], [17].

When we encounter a tumoral entity that resembles CDC, it is important to consider several major differential lesions that might be more oftenly mistaken with Bellini. The most common neoplasms that are part of this category are the urotelial carcinoma with glandular differentiation, papillary renal cell carcinoma, medullary carcinoma of the kidney, the mucinous and spindle cell carcinomas, tubulocystic carcinoma. Other lesions with a high importance in this matter are hereditary leiomyomatosis RCC and metastatic carcinoma from GI tract or lung [9].

Unfortunately, due to the fact that this tumor is very rare and has a non specific symptomatology that occurs late in evolution, the patients are being diagnosed in advanced stages. It is mentioned that the improvement of the prognosis depends of an early diagnosis, yet because of the situations mentioned above, most of those involved are undergoing surgery and receive treatment when they are in advanced stages or even present metastasis. Some studies reported a very poor survival range, with a median of 11 months [2], [14].

2. Material and Methods

We present the case of a 64 years old female patient committed in the Urology Department of the Clinical County Hospital Târgu-Mureș, Mureș County. The patient presented a right renal mass and the tumoral stage established by the clinicians was cT1N0M0. Nephrectomy was performed and the sample was sent to the Pathology Department for diagnosing and stadialization. The tissue was fixed in formaline and processed according to the protocols.

3. Results

The patient presented in the Urology department for gross hematuria and flanc pain. A CT scan was performed and a renal mass was seen at level of the right kidney.

On the gross examination, the nephrectomy specimen had dimensions of 150x80x60 mm, with renal parenchyma of 120x65 mm. We observed a tumoral mass involving both the medulla and the cortex, poorly circumscribed, with total dimensions of 26x23x22 mm. The color was yellow, with multiple hemorrhagic and necrotic areas.

Microscopically, on the Hematoxilin and Eosin stain, we observed an infiltrative tumoral mass which presented a tubular architecture, predominantly composed from a proliferation of tubular structures with different dimensions and forms. The majority of these structures were angulated, compressed, deformed and separated by a desmoplastic stroma in which we observed rare lymphocytes. The

tumoral tubular structures were lined by a single row of cubic cells with eosinophilic cytoplasm. The nuclei were increased in size and showed high pleomorfism. Nucleoli were also observed along with atypical mitosis. The grade of the tumor, based on the nuclei and nucleoli aspect, was 3 (according to the WHO/ISUP classification - nuclei visible at 100x magnification). Numerous areas of necrosis and hemorrhage were also present.

The tumor infiltrated the renal parenchyma, exceeded the renal capsule and extended into the perirenal lipomatous tissue, therefore the stage was set pT3aN0M0 (we had no information on the lymph nodes and dissemination towards other sites). No invasion of the blood vessels of the renal hilum was visible [15], [18].

The adjacent renal parenchyma showed changes characteristic for the chronic nephritis: hyalinized glomeruli, thick blood vesseled, thyroidization of the renal tubes and chronic inflammation composed mostly by lymphocytes.

The surgical resection limits were not infiltrated by the tumoral cells. No other lesions were seen on gross or microscopical examination.

To confirm the diagnosis of CDC, we performed a series of immunohistochemical reactions.

Table 1

Immunomarkers and the result of the reaction

Immunohistochemical marker	Result of the reaction
Vimentin	**Positive, cytoplasm**
CK 7	**Positive, cytoplasm**
34BE12	**Positive, cytoplasm**
EMA	**Positive, membranous**
CK 8/18	**Positive, cytoplasm and membrane**
CK 19	**Positive, cytoplasm and membrane**
E-cadherin	**Positive, membranous**
Bcl2	**Negative on tumoral cells**
P 63	**Negative**
CD 117	**Negative**
P 53	**Negative**

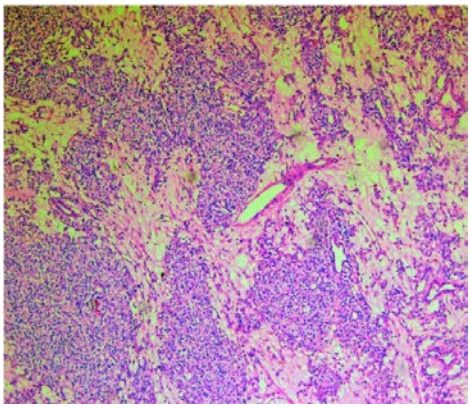

Fig. 1. *Bellini Duct carcinoma- Hematoxilin&Eosin stain, solid architecture*

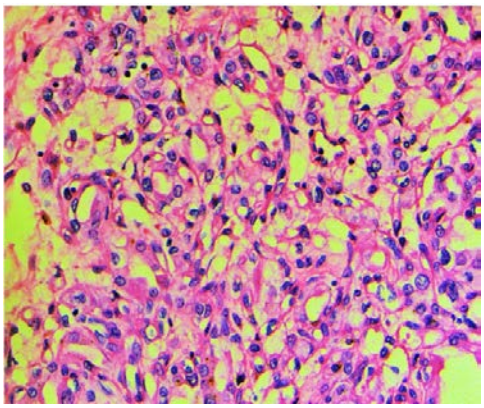

Fig. 2. *Bellini Duct carcinoma Hematoxilin&Eosin stain, high magnification*

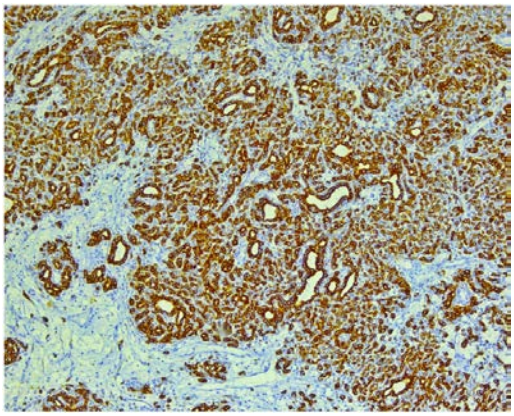

Fig. 3. *Immunohistochemestry- reaction with CK AE1/AE3*

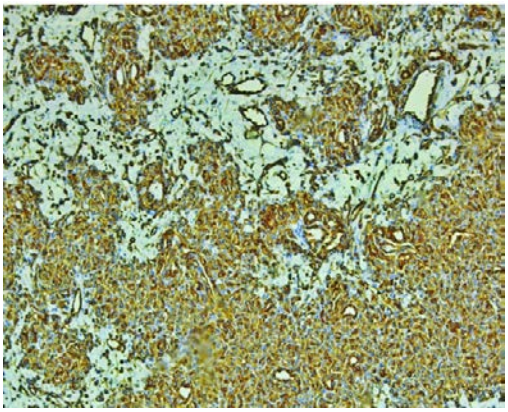

Fig. 4. *Immunohistochemestry- reaction with vimentin*

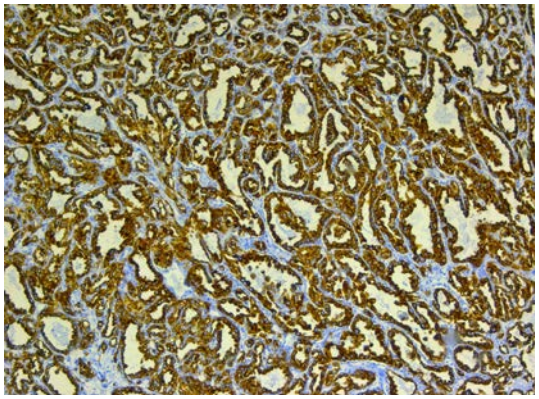

Fig. 6. *Immunohistochemestry- reaction with CK7*

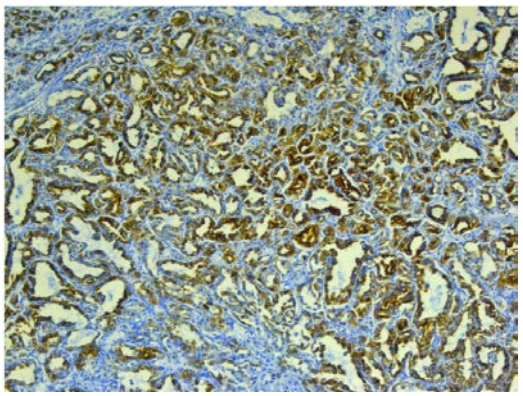

Fig. 7. *Immunohistochemestry- reaction with CK8/18*

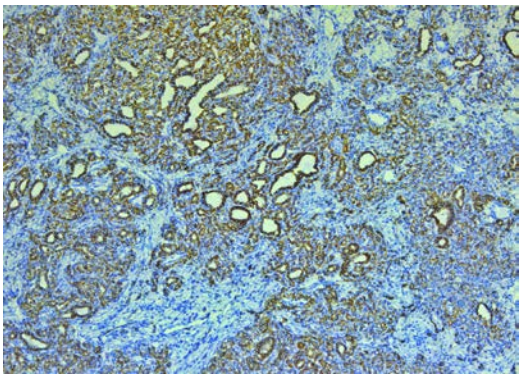

Fig. 7. *Immunohistochemestry- reaction with E-cadherin*

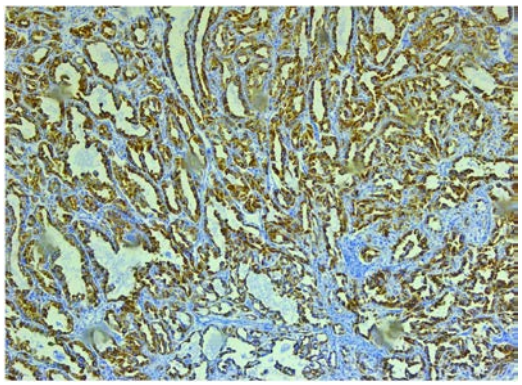

Fig. 9. *Immunohistochemestry- reaction with 34BE12*

4. Discussion

Collecting duct carcinoma (CDC) is a rare neoplasm, very hard to identify on the usual stain, that needs to be distinguished from all the other tumors with origins in the kidney. In literature, CDC is known to affect male patients mostly.

Our case is presenting a female patient, age 64, with a tumoral mass in the right kidney. The age of the patient is very close to the median age of the patients reported to present this pathology, but since CDC has a very wide interval of appearance, age is not a reliable factor [3], [12].

Studies describe CDC as an infiltrative, poorly circumscribed tumor that usually extends below the renal capsule. In our case, on the gross examination, the tumor appears as a poorly circumscribed mass, involving both the medulla and the cortex.

The histology of the tumor is highly variable, but it shows an infiltrative pattern. It was mentioned that the architecture of the neoplastic glands shows a tubular, papillar, solid or sarcomatoid pattern. Most authors described local or extended sarcomatoid transformation and tubulopapillar pattern. The number of mitoses is highly variable. According to Fuhrman grading system, most tumors were classified as grade III or IV, the lately WHO/ISUP classification also grades them as 3 or 4, depending on the sarcomatoid representation [1], [6], [10], [19, 20].

In our case, the tumor architecture was mostly tubular and no sarcomatoid transformation was observed. The cells presented high pleomorphism and were classified, according to WHO/ISUP, in grade 3. Desmoplasia is reported in most cases and also present in our sample, along with a low number of inflammatory cells - lymphocytes.

Immunohistochemistry is a very useful tool when facing CDC. In the past decades, there are several markers known to be expressed in this tumor, such as CTK

AE1/AE3 (a cocktail of keratins also known as pankeratin), CK7 (type II keratin with expression in a wide spectrum of epithelial tumors), 34BE12 (marker of urothelial origin), all of them positive in our case as well.

In time, more cases of CDC surfaced, therefore more markers were tested. It is stated that the tumoral cells express a larger number of markers than initially thought. However, many of these markers are not highly specific for this lesion and the diagnosis must be confirmed by using more than 2 or 3 antibodies. In our case, we chose a wide range of markers, most of them showing an intense expression. Besides the ones mentioned earlier, vimentin (mesenchymal marker), CK 8/18 (low molecular weight CK), CK 19 (smallest CK), EMA (epithelial membrane antigen) were also positive.

There are studies which mention the expression of p63 in 14% of CDC. Others describe an expression of bcl 2 in 4 out of 11 cases and a nuclear overexpression of p53. All these markers were negative in our case. CD 117 was also negative [4], [20]. Most studies sustain that E-Cadherin is usually negative in CDC, yet it can show positivity in rare occasions. In our case, E-Cadherin stain showed strong expression [11].

Regarding the follow-up of the patient, 6 months after the diagnosis her state was deteriorated. She began chemotherapy, the most used therapy method around the world. As mentioned before and proved in studies, this tumor has a high risk of mortality. The prognosis of the patient is very poor [16].

5. Conclusion

Collecting duct carcinomas are rare lesions, usually discovered in advanced stages. The diagnosis of these tumors requires a laborious work. It is important to exclude the other renal entities before raising the suspicion of Bellini and support the diagnosis with the use of immunohistochemistry. There is a limited number of cases described in the literature until now, all of them highlighting the particularities of CDC along with the tumor's heterogeneity in the usual staining with Hematoxilin & Eosin and in the immunohistochemical expression.

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