CLINICAL CASE

Bellini duct carcinoma: a case report and literature review

J. D. Farias-Cortés* and A. Castro-Alfaro

Urology Service, Hospital Regional “Valentin Gómez Farias”, ISSSTE, Zapopan Jal., México

KEYWORDS
Renal cell carcinoma; Carcinoma of the collecting ducts of Bellini; Immunohistochemistry; Outcome factors; Staging; Progression; Mexico.

Abstract
Kidney cancer is one of the first 10 malignant diseases in the adult. There are an estimated 270,000 new cases diagnosed annually worldwide, together with 116,000 deaths. In 1997 the Heidelberg classification recognized Bellini duct carcinoma as a separate subtype of malignant renal disease. Its diagnosis is based on specific pathologic characteristics, as well as on high molecular weight cytokeratin positivity, among others. Cytoreduction is the only consensus treatment, given that adequate results have yet to be seen with medical therapy. This pathology has one of the worst outcomes compared with the other kidney cancer histologic subtypes.

The aim of this study was to present a multicenter review using the Medline database to identify epidemiology, incidence, and mortality in relation to tumors of the collecting ducts of Bellini and to present a case from our hospital unit.

A 66-year-old man presented with pain in the right hypochondrium. Ultrasound imaging of the liver incidentally showed a right 5 x 5 cm renal tumor. A computerized tomography (CT) scan of the thorax, abdomen, and pelvis revealed a 5 x 4.5 cm right renal tumor with no evidence of local extension or metastasis of the disease. Nephrectomy was performed and histopathologic and immunohistochemistry studies were done, leading to the diagnosis of Bellini duct carcinoma.

PALABRAS CLAVE
Carcinoma de células renales; Carcinoma de túbulos colectores de Bellini; Inmunohistoquímica; Factores pronósticos; Mexico.

Carcinoma de ducto colector de Bellini: reporte de un caso y revisión de la literatura

Resumen
El cáncer renal es una de las 10 primeras entidades malignas en el adulto, globalmente se diagnosticará un estimado de 270,000 nuevos casos y morirán 116,000 anualmente. En 1997 se incorpora la clasificación de Heidelberg, en la cual se reconoce al carcinoma de ducto colector de Bellini, como una entidad maligna renal aparte de la convencional. Su diagnóstico es en base a características patológicas específicas, así como a la positividad de las citoqueratina.

* Corresponding author at: Cáncer N° 3992, Int. 602, Colonia Lomas Altas, Zapopan, Jal., México. Tel.: 33 1080 6462. Email: drdiegofarias@gmail.com (J. D. Farias-Cortés).
Introduction

In 2006, kidney cancer was responsible for the death of 12,840 individuals in the United States alone. The most common histologic subtype is clear cell carcinoma (90%), with a higher incidence peak in the 7th decade of life. It affects a slightly higher number of black men. In addition, it is one of the first 10 causes of cancer in all its presentations and represents approximately 3% of all neoplasias in the adult. An annual estimated 270,000 new cases will be diagnosed and 116,000 of these patients will die.

In 1997 the Heidelberg classification identified 4 kidney cancer subtypes, having observed differences in each one in their cytogenetic histology, aggressiveness, and outcome, thus dividing them into: conventional (clear cell) -the most common-, papillary, chromophobe, and collecting duct variants. The sarcomatoid variation was thought of as a state of progression of a high-grade tumor, but it is now clearly recognized as a different pathologic entity with its own biologic activity.

The majority of clear cell tumors of the kidney are formed from the epithelium of the proximal convoluted tubules; there is a neoplastic variant that develops in the distal collecting tubules (also called the Bellini ducts). This histologic variant was first described by Pierre Manson in 1970, and was initially called “Bellinian epithelioma”. The definitive name was first coined in 1979 by Cronie, and it was in 1985 that Fleming and Lewi described its clinical and histologic characteristics. In our present review of the literature, we found only a few case reports and multicenter studies that incorporated accumulated retrospective cases, due to the rareness of the finding.

The embryologic origin of the collecting tubules are the Wolffian ducts, which also give rise to the ureters and renal pelvis and calyces. Bellini duct carcinoma is quite rare and constitutes 1% to 2% of the renal epithelial tumors in the adult. It is more common in men (2/3), the mean presentation age of this type of tumor is 55 years, and it tends to be located predominantly in the medullary portion of the kidney due to its histologic origin.

Case presentation

A 66-year-old man, a pensioned welder, sought medical attention after having presented with stabbing pain in the epigastrium and right hypochondrium 15 days earlier. Suspecting gallbladder disease, his family physician ordered a liver and biliary tract ultrasound, and made the incidental discovery of a heterogeneous cortical image of the left kidney that was hypoechoic in its interior and measured...
approximately 5 x 5 cm (fig. 1). It was suggestive of a kidney tumor and therefore interconsultation with our Service was requested.

The patient had an important past medical history: the risk factors of high blood pressure of 15-year progression, treated with enalapril one tablet every 8 hours, as well as being chronically exposed to inhaled antimony products due to his previous work as a welder.6,7 He did not complain of any other chronic disease, weight loss, or constitutional symptoms and he stated he had never smoked. A simple contrast-enhanced abdominopelvic computed tomography (CT) scan revealed a heterogeneous 50 x 45.9 mm kidney tumor with invasion from the mid calyx to the cortical space. There was peripheral contrast-enhancement (figs. 2 and 3) with no evidence of thoracic or local metastasis and the bladder had no occupying lesions. Complementary laboratory tests reported Hb: 12.6 g, Hct: 35.6%, platelets: 142,000, leukocytes: 8.4, glucose: 120 mg, urea: 53 mg, creatinine: 1.04 mg, and bleeding time and liver function tests within normal parameters. Urinalysis: leukocytes 0 per field, erythrocytes 0 per field, and negative for bacteria, proteins, and nitrites.

Right nephrectomy was performed with no complications during or after surgery. Pathology report number 1735-12 was striking: “Pathologic specimen identified as right kidney was received. A firm, greyish-yellowish 5 x 5 cm tumor occupies the medullary region to the lower pole; upon 40 x 0.65 slice and stain with hematoxylin & eosin: neoplastic lesion that forms tubules, separated by an abundant fibroblastic stroma, covered by pleomorphic cells of abundant, eosinophilic cytoplasm and large round nuclei, surrounded by a prominent desmoplastic reaction; it extends from the medulla to Gerota’s capsule, without passing it, the renal hilum, and lymph nodes, with no neoplastic invasion” (fig. 4).

Immunohistochemistry with high molecular weight cytokeratins was carried out, showing intracytoplasmic positivity in the neoplastic cells for CK7 and CK10 (fig. 5), in addition to being positive for vimentin (fig. 6). Thus it was concluded to be Bellini duct carcinoma.

Discussion

Kidney tumors represent 3% of all malignancies, and of these, collecting duct tumors are the rarest and most aggressive. They make up 1% of the total of kidney tumors and their outcome is poor. Rapid identification together with an aggressive approach is their only protective survival factor.8 Nephrectomy is the treatment of choice and there is no universal chemotherapeutic regimen established yet, only case reports with different results. An extensive review follows herein regarding treatment, macroscopic and immunohistochemical diagnosis, and the outcome factors that can have an impact on patient survival.

Tomographic characteristics of the lesion: As described above, clear cell renal tumors develop from the proximal convoluted tubule, whereas the Bellini ducts arise from the collecting tubules and therefore emerge from the medulla of the kidney. There are no specific findings that can differentiate a clear cell renal tumor from a collecting tubule one, except that the latter are found more toward the medulla, their presentation is slightly more heterogeneous, and they mainly involve the renal sinus, with invasive growth preserving the renal contour, as well as eventual small cystic images within the same lesion.9

Treatment: There is no consensus as to the therapy to be followed after nephrectomy. Several articles have made
proposals ranging from alpha interferon combined with interleukin 2, to combinations of gemcitabine and cisplatin, based on the great immunohistochemical, embryologic, and cytogenetic similarity with transitional cell carcinoma. In the multicenter studies where this latter combination is used, a 1,250 mg/m² dose of gemcitabine and 70 mg/m² of cisplatin had a complete response of 26%, an estimated progression-free survival of 7.1 months, and an improved 10.5 month overall survival. Hematologic toxicity was the main undesirable side effect characterized by neutropenia and thrombocytopenia in 52% and 43%, respectively. It was necessary to change to carboplatin in 22% of the cases, arriving at the conclusion that survival would be inversely proportional to the number of metastases, as well as to treatment intolerance. In another article, gemcitabine was used in combination with a new agent called nedaplatin (similar to cisplatin but less nephrotoxic). There was partial initial improvement in one patient with the granulocyte colony stimulating factor-producing tumor as a paraneoplastic syndrome; the patient had an initial reduced leukemoid reaction, but then had tumor recurrence followed by death.

Histologic characteristics of collecting duct tumor: Macroscopically, it tends to be a solid greyish lesion that is diffuse and irregular, although on some occasions it preserves the renal contour. The papillae are usually deformed and protrude from the renal pelvis. The following can be specified as major characteristics: medullary pyramids compromised with small lesions, irregular tubular architecture, marked desmoplasia, high grade hobnail cells, positivity for high molecular weight cytokeratins (CK7, CK10), positivity for the Ulex europeaus lectins, epithelial membrane antigen, lysozyme, and vimentin. In addition, there is no presence of synchronous urothelial carcinoma. Reported as minor criteria are: centrally located large lesions, papillary architecture with fibrosis and desmoplastic stroma, inflammatory stroma with neutrophils, extrarenal extension and vascular infiltration, and mucin positivity.

Among other new immunomarkers is the laminin-5 molecule. It consists of an alpha 3, beta 3, and gamma 2 chain that is expressed in the epithelial tissue of the collecting ducts, thus differentiating itself from tissue from other parts of the kidney. Although in some cases it can be positive for papillary tumors, this differentiation should be made through expression, in addition to high molecular weight cytokeratins such as CK7, CK10, or CK19. Positivity for laminin-5 can be related to the aggressiveness of this tumor, and so it should be taken into account in studies that include a greater number of cases.

Among the cytogenetic characteristics found in the patients with this type of tumor are, in particular, the deletions on 1p, 8p, 9p, 16p, and 22p, as well as chromosome X13q gain; a study carried out at various centers in Germany—the largest analyzing the cytogenetics of the collecting duct tumors found up to now—that included 29 specimens, arrived at the conclusion that opportune diagnosis and early surgical treatment were more important than the results of cytogenetic gain or loss. Other specialized research centers have found monosomes 18 and 21, as well as the losses described above; in one study, alterations, especially in chromosome 1, were found in all the samples analyzed, and aneuploidy was observed in 90%. It seems that deletion on chromosome 8p is the most widely found chromosome anomaly, since it appeared in all the articles on cytogenetics described in this review, along with being a poor outcome factor, given the aggressive behavior of the tumors that presented with this abnormality. The VHL and RB gene mutations have been sporadically reported as anecdotal cases, and conclusions about their role in this type of tumor have not yet been drawn. The expression of the p53, p27, and Bcl2 proteins has been observed in only 27% to 36% of the cases and therefore has not had any significance on outcome. A larger number of samples is needed for continuing cytogenetic research.

Differential diagnosis: due to the histologic similarities to the other subtypes, their differences should be very well defined in order to make the correct diagnosis, especially in relation to determining the outcome of each pathology. The main histopathologic characteristics are shown in table 1.

Outcome: in all the studies reviewed for this article, Bellini duct carcinoma is recognized as having one of the worst outcomes of all the histologic subtypes of kidney cancer, with a mean survival of approximately 13 months from the time of diagnosis (0-59 months). In one of the most recent case series that studied a larger number of patients,
Bellini duct carcinoma

The sarcomatoid variant had the worst outcome of all the subtypes, with a survival of 6 months from the time of diagnosis (6-68 months).

Tumor stage and undifferentiated nuclear grade in the sarcomatoid subtypes and collecting duct carcinoma are detected in the most advanced stages at the time of diagnosis. There is the probability of finding stage T3 and T4 and a Fuhrman grade 3 in 55.7% of the patients with collecting duct carcinoma, compared with the probability of T3 or T4 in 28% or nuclear grade 3 in 17.6% of the cases with the papillary subtype, resulting in a worse outcome, as mentioned above, for patients with this type of collecting duct carcinoma; the survival rate at 5 years is only 6%.9

The histologic subtype that has been the subject of this article has been shown to have a greater propensity for local propagation (28%) and metastasis (32.1%) at the time of diagnosis and to have a greater appearance of lymph node disease (15%), as well as recurrence. The main metastatic sites are the lung, bone, liver, brain, and parietal pleura.19 If survival is compared between the patients with clear cell tumor and collecting duct disease, both having a poorly differentiated or metastatic tumor, the Bellini tumor would have a slightly worse outcome than the conventional one.9

Conclusions

Collecting duct carcinoma is a rare entity that must be differentiated from the other malignant diseases among the tumors of the kidney by means of their histopathologic characteristics as well as their specific immunohistochemical characteristics, because it does not share the same progression and outcome as the conventional renal cell tumor.5 Early diagnosis and adequate radical treatment are the most important outcome factors, given that the largest case series have observed that as long as the tumor is localized, its complete surgical removal in the early stage is the definitive treatment.

More clinical studies with large case series must be conducted and compared with those from the different international oncologic centers, so that a consensus on the systemic treatment of the disseminated disease can be arrived at. Presently, there are only a few clinical reports in which the apparent best therapy is the same as that used for disseminated urothelial cancer, perhaps due to the cytogenic and embryologic characteristics shared by these 2 types of tumors.

Conflict of interest

The authors declare that there is no conflict of interest.

Financial disclosure

No financial support was received in relation to this article.

References


Table 1 Differential diagnosis of collecting duct cancers

<table>
<thead>
<tr>
<th>Tumor subtype</th>
<th>Histologic characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary renal cell carcinoma</td>
<td>No dysplasia of collecting duct epithelium; psammoma bodies and macrophages; LeuM1 positive and mucin negative.</td>
</tr>
<tr>
<td>Urothelial carcinoma with glandular differentiation</td>
<td>Rarely invasive.</td>
</tr>
<tr>
<td>Urothelial adenocarcinoma of the pelvis</td>
<td>Usually mucinous; negative for vimentin.</td>
</tr>
<tr>
<td>Urothelial carcinoma of the gastrointestinal tract and lung</td>
<td>Well-defined; with multiple lesions.</td>
</tr>
<tr>
<td>Renal medullary carcinoma</td>
<td>Subtype of rapid growth that presents in the medulla; more common in black men; associated with falciform cells.</td>
</tr>
</tbody>
</table>


