CLINICAL CASE

Kidney cancer metastatic to the testis

J. D. Farias-Cortés*a,b, A. Scavuzzob, M. A. Jiménez-Ríosb, A. Castro-Alfarob and J. C. Navarro-Vargasb

*a Hospital Regional del ISSSTE “Valentín Gómez Farias”, Zapopan, Jal., Mexico
b Uro-oncology Service, Instituto Nacional de Cancerología, Mexico City, Mexico

KEYWORDS
Kidney cancer; Clear cell renal carcinoma; Metastatic pattern; Progression, Mexico

Abstract  Kidney cancer is one of the first 10 malignant entities in the adult. Its overall diagnosis is estimated at 270,000 new cases per year with 116,000 deaths. The sarcomatoid variant can be found in 1% to 8% of the patients with renal tumor, typically affecting patients between the ages of 56 and 61 years. There are symptoms at the time of diagnosis in up to 90% of patients due to metastasis, and the most common are pain and hematuria; multiple metastases are present in 47% of patients from the beginning of evaluation. Median survival is 13 months from the time of diagnosis, and 6 to 9 months when there is metastasis.

The aim of this work was to present a multicenter review article using the MEDLINE® database to identify epidemiology, incidence, metastatic potential, and mortality rate of the sarcomatoid variant of renal tumors, as well as to describe a case report from our hospital unit.

A 65-year-old man had a 10-year history of intense smoking and was recently diagnosed with high blood pressure. His illness began with painless, clot-forming gross hematuria. An abdominal computed tomography (CT) scan showed a tumor on the lower pole of the left kidney with no apparent evidence of metastasis. He underwent radical nephrectomy in August 2012 that reported a T4 N0 M0, 12 x 10 cm sarcomatoid tumor. He was scheduled for follow-up but appeared at the emergency department 2 months after surgery with an increase in volume of the left testis, asthenia, adynamia, medium-effort dyspnea, submentonian adenopathy, and general malaise. A chest CT revealed intense metastatic activity and a testicular ultrasound showed a heterogeneous image with hypoechoic areas. The patient underwent radical orchietomy that reported a metastatic sarcomatoid renal cell tumor and he was referred for adjuvant chemotherapy. One month and a half after his latest surgery, the patient was readmitted with a frankly deteriorated status and mild-effort dyspnea. He was referred to home care for maximum benefit.
Introduction

Kidney cancer was responsible for the deaths of 12,840 persons in the United States, alone, in 2006, and the most common type is renal cell carcinoma (90%). Its peak of greatest incidence is in the seventh decade of life and there is a slightly higher incidence in African American men.1

Kidney cancer is one of the 10 most common cancers, and renal cell carcinoma represents 3% of all adult neoplasias.2 It is estimated that 270,000 new cases of kidney cancer will be diagnosed annually worldwide and 116,000 will result in death.3

In 1997 the Heidelberg classification was described. It provides 4 subclassification types of renal cell cancer from the observed differences in histology, cytogenticity, aggressiveness, and outcome among them, and they are: conventional (clear cell), the most common; papillary; chromophobe; collecting duct; and the sarcomatoid variant. The latter was thought to be a state of high-grade tumor progression, but it is now viewed as a different pathologic entity with its own clearly recognized biologic activity. A nuclear Fuhrman grade 4 has been found in up to 94.7% and with distinct metastasis at the time of diagnosis in 55.3% vs. 10%-30% of the cases with clear cell renal cell carcinoma.4

The sarcomatoid variant can be found in 1% to 8% of the patients with renal tumor and it typically affects patients between the ages of 56 and 61 years, with tumors between 9-11 cm in diameter at the time of diagnosis.3 Ninety percent of the patients have symptoms at the time of diagnosis due to metastasis, the most common of which are pain and hematuria. Forty-seven percent have multiple metastases at the beginning of their evaluation.5 The ability to diagnose this variant is poor, and it is also difficult through fine needle aspiration biopsy.7

Case presentation

A 65-year-old man born in Zurich, Switzerland, and residing in Mexico City was a retired public works supervisor. His family medical history was unremarkable in regard to his case. He had recently been diagnosed with high blood pressure that was being treated with ACE inhibitors. He had been an intense smoker for 10 years, but had quit smoking 20 years ago. His disease onset began in May 2012 when he sought medical attention due to general malaise and one episode of self-limited gross hematuria. He had no abdominal pain or weight loss at that time and his ECOG score was 0. Therefore, upon his arrival at our service an abdominal computed tomography (CT) scan was ordered. It revealed a 12 x 17 x 14 cm left renal tumor dependent on the left kidney at the mid portion and lower pole. Contrast enhancement was > 20 HU and the tumor was staged as Tc2b
(due to size), with no vascular involvement. Preoperative laboratory tests were carried out and showed normochromic, normocytic anemia (Hb 9.7 g). A chest-x-ray revealed no evidence of metastatic activity. The patient underwent radical nephrectomy on August 14, 2012, with no problems during surgery. After a short hospital stay he was sent home. During his control visits, the histopathologic study was obtained that reported: clear cell renal cell carcinoma with a sarcomatoid pattern in the entire tumor volume, a 20% area of necrosis central to the tumor, Fuhrman 4, 12 x 10 cm tumor size, lower pole location, and infiltrating the renal sinus, capsule, perirenal fibroconnective tissue, and Gerota’s fascia; the vascular structures of the renal hilum and the adrenal gland had no evidence of neoplastic invasion and the resection surgical margin was free from neoplasia. In conclusion the tumor was T4pN0M0. Follow-up was begun and the patient was scheduled for thoracic-abdominal CT and general laboratory tests. However, he was readmitted to the emergency department 2 months later presenting with asthenia, adynamia, medium-effort dyspnea, submentonian nodule, and increased volume of the left testis. A chest x-ray in 2 projections clearly showed multiple radio-opaque images (fig. 1). In addition, an ultrasound of the gonads was carried out revealing a heterogeneous image of the entire structure with marked suspicion of neoplasia. The vasculature of the left testis was enlarged and there was important tortuosity of the pampiniform plexus (figs. 2, 3, and 4); the contralateral testis was normal. Thoracic-abdominal CT showed multiple hyperdense, parenchymal lesions larger than 3 cm in the pulmonary parenchyma and there was no evidence of pleural space effusion (figs. 5 and 6).

Preoperative evaluation resulted in ASA II, Goldman II, and Kanofsky 80% and preoperative laboratory tests showed anemia (Hb 9.1 g, Ht 28.8%) once again, with creatinine of 1.5 mg. Electrolytes, coagulation times, liver function test and lactate dehydrogenase were in normal parameters and the ECOG score was 2. The patient was transfused preoperatively with one red blood cell package. Radical orchectomy was performed, producing a firm specimen that was not adhered to the scrotum, with a free spermatic cord. The patient was released from the hospital, and seen as an outpatient with the pathologic report: testis with metastatic sarcomatoid renal carcinoma, tumor size of 4.8 x 3.4 cm, and spermatic cord free of neoplastic cells. For evaluation and treatment he was referred to the Medical Oncology Department to begin chemotherapy and to the Head and Neck Department for biopsy of suspected adenopathy from submentonian metastatic disease. The patient returned to the Emergency Department in December of the same year with general malaise, a clearly deteriorated state, and weight loss of more than 20 Kg from his initial weight, asthenia, hypodynamia, generalized paleness, and an ECOG score of 3. His relatives decided to continue only with palliative therapy at home, for maximum benefit. The patient died 20 days later.

Discussion

In the first half of the last century “renal sarcoma” was known as that poorly differentiated tumor in patients in very advanced stages. However, in later studies the same variant was observed in different types of tumors, and therefore was called “the final stage of kidney cancer” as the last undifferentiated tumor stage. That are 2%-10% depending on the case series, it is very common to find a pure sarcomatoid pattern in the 2% to 10% of patients, depending on the case series, that present with unclassifiable tumors. Besides identifying a sarcomatoid pattern in any renal tumor variant, there were no changes in outcome or treatment. Despite the different regimens employed, they all resulted in a poor outcome. Therefore it became necessary to identify this variant as a different pathologic entity. Although the majority of cases have very

Figure 1  Chest x-ray with multiple radio-opaque paramediastinal images and tracheal air column deviation.
poorly differentiated cellular nuclei, about 30% of sarcomatoid tumors have nuclei with Furhman 1 and 2 grades, suggesting the emergence of an independent cellular separation, rather than an undifferentiated entity. It should be mentioned that numerous studies indicate that the sarcomatoid pattern is more prevalent in men (approximately 75%).

Histology

Macroscopic sarcomatoid renal tumors are generally described as: firm, voluminous, and of white to greyish tones when cut. This variant is mainly associated with clear cell tumor, up to 8.7%, although these components can be observed in the chromophobe, papillary, and collecting duct types; there is necrosis in up to 90% of the patients. However, it is determined as an independent variant due to its metabolic and potentially metastatic activity mentioned before.

Microscopically, sarcomatoid components are described as images similar to fibrosarcomas, with intersections of malignant fusiform cell fascicles. In addition there is the possibility of finding undifferentiated pleomorphism similar to malignant fibrous histiocytoma (fig. 7). It does not generally require the support of special studies such as electron microscopy, immunohistochemistry, or molecular genetics for its diagnosis. Genetically, a complex chromosomal gain and loss can be observed, with the absence in 13q (75%) and 4q (40%).

Metastatic pattern

In patients with metastatic disease, it is most common to observe a purely sarcomatoid pattern in the sample in 97% of the patients, regardless of the primary differentiation at the place of origin. In the opposite case, if metastasectomy is performed first and no sarcomatoid pattern is found, it will be very difficult to find it in the primary tumor. Among the most common sites of metastasis are: regional lymph node chain 60%, lung 11%, liver 7.7%, and bone 3.8%. The percentage of sarcomatoid variant in the specimen is also important, because metastasis and time of death from the disease are more common in those patients with a percentage above 30%. One study states that alterations in the p53 gene are 5 times higher in regions with sarcomatoid differentiation, in addition to expression of more markers such as Ki67, VEGF, vimentin, and actin.

Renal tumors can metastasize in virtually any part of the body. There are really very few studies that investigate the
mo
test common sites of the lesions according to their histologic subtype. The majority of the time the conclusion is: clear cell tumors are the principal metastasizing tumors, mainly involving the regional lymph nodes, but they also metastasize to the lung. Papillary tumors metastasize mainly to the regional lymph nodes, as well as to less common sites. Chromophobe tumors tend to metastasize to multiple sites, with a greater affinity for the liver, adjusting the incidence percentage (table 1).16

In various studies that followed, the conclusion was that outcome is less favorable when there are multiple metastasis sites compared with a single site. The result was statistically significant ($p<0.001$), with a median 13-month survival despite surgical treatment followed by adjuvant therapy vs. survival of up to 31 months in those patients with only pulmonary metastasis.17 Distant metastasis to rare sites such as the stomach,18 gallbladder,19 oropharynx,20 left ventricle,21 skin,22 tonsils,23 spleen,24 pancreas,25 pituitary gland,26 thyroid,27 breast,28 gemellus muscle,29 duodenum,30 and testis31 have been reported as isolated clinical cases.

The incidence of metastasis from other organs to the testis is from 0.3% to 3.6%, the prostate being the most common.22 Reports state that the majority of cases are due to clear cell tumors, though chromophobe tumors have also been reported.31 They are generally ipsilateral and the left side is predominant, suggesting infiltration from the renal vein and migration of the tumor coagulate to the testicular vein as a possible cause.33

Local and systemic treatment

Due to the biologic nature of this tumor, radical therapy is the most accepted treatment when dealing with localized disease. The role of partial nephrectomy in these patients has not been analyzed due to the lack of prospective studies. Because it is a highly invasive and aggressive tumor, complete resection of the kidney unit is recommended.9 Due to the tangible absence of benefits in performing lymphadenectomy in patients undergoing radical nephrectomy with evidence grade 1A, it is not usually done, although some authors recommend it if the adenopathies are obvious, because they have been shown to be positive in up to 33%.34 Based on an evidence level of 1, cytoreduction is beneficial when speaking of systemic treatment of metastatic renal carcinoma with targeted therapy.35

In regard to systemic management, various regimens have been used with isolated reports of either partial or complete response.9 Interleukin 2 has been used in immunotherapy and some cases have shown a mean survival of 10 months vs. 9 months in those patients that were not treated with anything; up to the present there are no long-term survival reports.36 In the patients treated with chemotherapy, those that have benefitted the most are the patients that received a combination of doxorubicin and gemcitabine; one patient was reported to have had a complete response and an over 8-year survival, albeit this was an isolated report.37 Patients undergoing antiangiogenic therapy with sunitinib have shown very limited benefit with a 4-month survival rate.38 The results in patients treated with tyrosine-kinase inhibitors have not been very promising, with partial results of 19%, progression-free survival of 5.3 months, and overall survival of 11.8 months. A better result was seen in the patients previously treated with chemotherapy and in those with a percentage of sarcomatoid tumor under 20%.39 In relation to mTOR therapy, the sarcomatoid variant has not been analyzed separately in the studies conducted.40 Cetuximab, geldanamycin, and bortezomib are drugs that have been used experimentally, and the final results in the follow-up reports are pending.41

Conclusions

Patients presenting with any percentage of tumor with sarcomatoid differentiation have a poor prognosis from the outset, compared with those that have tumors with other variants. Additionally, the presence of different pathologic characteristics such as renal capsule invasion, percentage of necrosis within the primary tumor, number of metastases, nuclear differentiation grade, and vascular invasion make up a primordial disease-specific survival pattern. Therefore it is necessary to carry out a thorough study of the surgical specimen in order to precisely determine the severity of the oncologic manifestation. We must also keep the functional
status of the patient in mind, because there is a lower survival rate when the disease presents with a previously comorbid patient. In regard to treatment, it is necessary to point out the poor gain in overall survival in relation to cytoreduction in advanced stage patients; therefore, management should be well planned out before proposing risky and radical treatment, and both patient and relatives must be informed as to the patient’s real status.

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   | The most common sites of metastasis according to histologic subtype. |
|-----------|---|---|---|
|           | Clear cell | Papillary | Chromophobe |
| Non-regional lymph nodes | 3.8% | 10.3% | 5.6% |
| Pulmonary | 53.6% | 33.3% | 33.3% |
| Bone      | 25.3% | 20.5% | 16.7% |
| Liver     | 9.7% | 18% | 33.3% |
| Other sites | 22.4% | 35.9% | 33.3% |
| Multiple sites | 15.6% | 18% | 22.2% |


