Dedifferentiated Chromophobe Renal Cell Carcinoma With Massive Osteosarcoma-Like Divergent Differentiation: A Singular Entity in the Spectrum of Retroperitoneal Calcifying Tumors

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Sarcomatoid change in renal cell carcinoma is the result of the dedifferentiation of the “parent” tumor into a high-grade malignancy characterized by sarcoma-like features and associated with an accelerated clinical course and poorer prognosis. Any of the renal cell carcinoma subtypes can undergo sarcomatoid dedifferentiation, with the chromophobe variant being the most prone. The present report describes the case of a woman affected by a classic chromophobe renal cell carcinoma that developed dedifferentiation accompanied by a very rare osteosarcoma-like divergent differentiation, which constituted about 90% of the entire retroperitoneal mass. In addition to presenting the relevant imaging, histopathological, and immunohistochemical findings, this article briefly discusses the main differential diagnosis of retroperitoneal ossifying/calcifying masses, which could give rise to diagnostic problems either in small biopsies or at imaging.

Keywords: chromophobe renal cell carcinoma; dedifferentiation; osteosarcoma-like divergent differentiation; histopathology; computed tomography; scintigraphy

Renal cell carcinomas (RCCs) are a heterogeneous group of solid tumors that represent about 3.5% of all the malignant neoplasms in adults. Over the last few decades, their incidence has progressively increased, in all likelihood as a consequence of the general increase in average life expectancy of the population and the use of more accurate diagnostic imaging techniques, this fact entailing a greater number of incidentally discovered small renal masses.1 Interestingly, in addition to this increase in localized tumors, there has also been a significant upward trend in the incidence of advanced renal tumors (ie, >7 cm and/or with renal vein involvement) and disease mortality. Speculations on potential novel exogenous carcinogens have been made to provide an explanation for these seemingly contradictory trends in epidemiology.2

Sarcomatoid RCC is an acquired histological variant that can affect any of the RCC subtypes and is usually characterized by large size, poor prognosis, and marked cytological atypia, with highly atypical spindle cells reminiscent of a sarcoma.3 In comparison with the other RCC histotypes, patients suffering from chromophobe RCC are said to be slightly more susceptible to experience high-grade sarcomatoid transformation.4

Here, we report the case of a woman affected by chromophobe RCC who developed dedifferentiation
accompanied by osteosarcoma-like divergent differentiation. The main differential diagnosis of retroperitoneal ossifying/calcifying masses is also discussed.

**Case Report**

A 73-year-old woman was admitted to the hospital because of weakness, increasing abdominal pain, and hematuria. On palpation, a sizeable mass located in her left abdominal side was identified. Computed tomography (CT) scanning (Figures 1A, 1B, and 1C) and scintigraphy (Figure 1D) highlighted a heterogeneous mass (19 × 12 × 23 cm) apparently arising from the left kidney, as well as a left lung nodule highly consistent with a metastasis. In particular, CT showed that this huge neoplasm relegated the kidney upper-medially into the retroperitoneum. The tumor was hypervascular and characterized by a nonhomogeneous pattern (resulting from the admixture of viable and necrotic components), with several aspects
consistent with either calcification or ossification, the largest one ($3.5 \times 2.5 \text{ cm}$) located at the lower renal pole level.

After surgical excision, this lesion was immediately fixed in a 10% formalin-buffered solution for 48 hours and embedded in paraffin. The paraffin tissue blocks were cut into 5-μm sections and stained with hematoxylin and eosin. Additional 5-μm histological sections were kept for the immunohistochemical analysis, which was performed using the following primary antibodies: anti-vimentin (NeoMarkers, Fremont, CA, 1:500), anti-cytokeratin pool (Dako Cytomation, Glostrup, Denmark, 1:100), anti-S100 (Biogenex, San Ramon, CA, 1:800), anti-CD10 (Dako Cytomation, 1:50), and anti-epithelial membrane antigen (EMA; Dako Cytomation, 1:100).

Histologically, about 10% of the neoplasm was composed of a classic chromophobe renal cell carcinoma with medium-sized polygonal cells characterized by prominent cell membranes, eosinophilic cytoplasm, nucleolated nuclei, and frequent perinuclear clear halos (Figure 2A). Passing through a borderline zone with increasing cellular atypia (Figure 2B), the chromophobe component turned into a high-grade sarcomatoid neoplasm with diffuse interstitial osteoid deposition, large amounts of atypical mineralized bone (Figure 2C), and large areas of necrosis and hemorrhage. Islands with undifferentiated high-grade spindle-cell features and necrosis were additionally detectable throughout the mass. In the sarcomatoid component, the frequently atypical mitotic figures accounted for an average of 26 per 10 high-power microscopic fields. The diffuse immunohistochemical expression of vimentin, EMA, and cytokeratin pool (Figure 2D) by the sarcomatoid cells along with the blatant association with a pure RCC subtype, steered our diagnosis toward a “chromophobe RCC with dedifferentiation and osteosarcoma-like divergent differentiation.”3 The sarcomatoid component showed no positivity for either S100 or CD10 primary antibodies. This woman died shortly afterward as a consequence of the disseminated disease. No autopsy was performed.

Discussion

Dedifferentiation represents a well-known potential pejorative event within an RCC, the sarcomatoid change in the chromophobe histotype accounting for as many as 9% of the cases.5,6 Because of the aggressive behavior of this variant, the overall 5-year survival is only about 20%, and although the great majority of sarcomatoid RCCs are diagnosed when already advanced, after adjusting for stage, sarcomatoid transformation is a significant predictor of poorer prognosis.3 Survival at 2 years for patients with chromophobe RCC without sarcomatoid component is 95.3% and this plummets to 27.8% in the presence of a dedifferentiated component.4

The reason why chromophobe RCC, among the different RCC variants, has the greatest propensity to dedifferentiation has not yet been clarified. The genetic hallmark of chromophobe RCC is the loss of multiple chromosomes (ie, 1, 2, 6, 10, and 17), this leading to hypodiploid tumor cells with a very low number of chromosomes. These hypodiploid cells may undergo polyploidization by doubling their chromosomes and potentially give rise to genetic abnormalities responsible for the sarcomatous transformation.8 It has recently been shown that both the epithelial and sarcomatoid components of sarcomatoid chromophobe RCC are characterized by different genetic abnormalities compared with pure chromophobe RCC, thus suggesting that multiple chromosomal gains are key factors in the sarcomatoid transformation.9 However, the precise sequence of genetic events involved in this transformation is far from being fully understood.

The osteosarcoma-like divergent differentiation is a very uncommon evolution in a RCC, which to the best of our knowledge it has been reported once.10 In a series of 101 sarcomatoid RCC, de Peralta-Venturina et al5 found that the sarcomatoid dedifferentiation with divergent differentiation could be fibrosarcoma-like (54%), malignant fibrous histiocytoma-like (43%), rhabdomyosarcoma-like (2%), or undifferentiated (1%), whereas there were no cases showing osteoid matrix deposition. When discovered, the tumor under discussion was largely infiltrating the retroperitoneal soft tissues and had already caused a lung metastasis (WHO stage IV).3 The diagnosis of sarcomatoid RCC was mainly made on the basis of the synchronous presence of the well-differentiated chromophobe and dedifferentiated components. At their boundary, these shared a transition zone composed of gradually more atypical and spindle-shaped tumor cells. Furthermore, the presence of this “transitional” area made the possibility of a collision tumor very remote. The broad immunohistochemical expression of both cytokeratin
and EMA by the sarcomatoid elements further helped us in steering our diagnosis towards such an exceptional tumor, although positivity for epithelial markers has previously been described in otherwise pure osteosarcomas.\(^{11}\)

In cases of this sort, especially when dealing with small biopsies, the pathological differential diagnosis can be arduous. This includes retroperitoneal neoplasms with an osteosarcomatous phenotype, either originating from or secondarily involving the kidney. Renal, extraskeletal, or metastatic osteosarcomas are exceedingly rare malignancies.\(^{11,12}\) Their identification usually depends on the amount of stromal mineralized osteoid. Conventional radiographs may help in diagnosing these lesions by showing variable cloud-like areas of opacity which, on CT, present as a heterogeneously enhancing mass with barely visible-to-diffuse mineralization.\(^{13}\) Undifferentiated high-grade pleomorphic sarcoma (so-called malignant fibrous histiocytoma) is a malignancy whose line of differentiation is not codifiable by applying currently available technologies. In addition to areas of haemorrhage and/or necrosis, this sarcoma may sometimes exhibit metaplastic bone in the context of a highly heterogeneous mass.\(^{11}\) Dedifferentiation towards a nonadipocytic sarcoma is a frequent event occurring within a well differentiated liposarcoma. Its dedifferentiating component may show either

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**Figure 2.** Histopathology. A, The chromophobe renal cell carcinoma characterized by nesting arrangement of its cells. B, Transitional area from the chromophobe carcinoma (lower right) to the high-grade sarcomatoid dedifferentiation (upper left). C, The great majority of the high-grade component displays an osteosarcoma-like appearance. D, In the dedifferentiated component, some tumor cells are immunohistochemically positive for AE1/AE3 cytokeratins. A, B, and C: hematoxylin–eosin stained. D: hematoxylin counterstained. A, B, C, and D: original magnification \(\times10\), bar scale is 300 \(\mu\)m.
zonal calcification/ossification or develop as a true osteosarcoma. The identification of a fatty tumor (either histologically or on magnetic resonance imaging), consistent with a well-differentiated liposarcoma, juxtaposed with the nonlipomatous component, is usually indicative of a dedifferentiated liposarcoma. Intra-abdominal myositis ossificans is a rare benign process characterized by reactive bone formation in the context of the intra-abdominal soft tissues. Due to the irregular new bone deposition, its interpretation may be ambiguous either with conventional x-rays or CT. However, a histopathological picture characterized by spindle cells and trabeculae of reactive bone with marked benign osteoblast rimming, will allow us to made a correct diagnosis in the great majority of cases. At imaging, some retroperitoneal nonsarcomatous neoplasms such as adrenal cortical carcinomas and teratomas (either mature or immature) may display calcifications and therefore these also have to be taken into consideration within the radiological differential diagnosis.

In conclusion, sarcomatoid transformation is a predictor of shorter survival in RCC. Osteosarcoma-like divergent differentiation within a renal cell carcinoma is a very rare event. However, it should be taken into account when dealing with retroperitoneal renal/perirenal masses characterized by coarse calcification.

References