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Case report

Renal cell carcinomas' hidden challenge: Sarcomatoid differentiation uncovered

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Abstract

Renal cell carcinoma (RCC) with sarcomatoid differentiation accounts for 4% of all RCC cases. This aggressive variant is characterized by spindle-shaped tumor cells and carries a high risk of metastasis and poor outcomes. Accurate diagnosis is crucial due to its aggressiveness and the limited treatment options. A 55-year-old male presented to the nephrology department with right lumbar pain, hematuria, and burning micturition. Radiology showed an enlarged right kidney with a hetero-echoic mass (7x5x2cm) across the mid and lower pole. He underwent right nephrectomy followed by histopathological examination and immunohistochemistry. Gross examination showed a well-circumscribed lower pole lesion along with hemorrhagic areas in the upper pole. Microscopy revealed spindle-shaped tumor cells in an inflammatory background, consistent with the diagnosis of RCC with sarcomatoid differentiation. Immunohistochemistry was positive for both epithelial and mesenchymal markers. Thus, diagnosed as renal cell carcinoma with sarcomatoid differentiation. ''Sarcomatoid renal cell carcinoma" is not a distinct subtype of RCC as it occurs with all histologic subtypes of RCC. It originates from epithelial-mesenchymal transition. Even a small component of sarcomatoid differentiation independently predicts poor survival compared to primary RCC. Therefore, accurate documentation of sarcomatoid differentiation in pathology reports is vital for precise prognostic assessment and guiding treatment strategies. More research is needed on sarcomatoid renal cell carcinomas (SRCCs) due to ineffective treatments. Immune checkpoint blockade therapies show promise, but large-scale efforts are crucial for better solutions.

Key words: Epithelial-mesenchymal transition, Heteroechoic mass, renal cell carcinoma, Sarcomatoid differentiation, Spindle-shaped cells

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Renal cell carcinoma represents a large component of kidney cancers, with wide range of microscopic and clinical features. Among its various subtypes, renal cell carcinoma with sarcomatoid differentiation grabs our attention due to its distinct histological features and clinically challenging nature. This variant involves the transformation of conventional renal cell carcinoma cells into spindle-shaped cells, which closely resemble sarcoma leading to more aggressive disease pattern. In sarcomatoid renal cell carcinoma, the tumor cells undergo a transformation where they acquire a spindle shape, a hallmark of sarcoma-like cells. The spindle-shaped cells within SRCC often form bundles or fascicles, and their presence can be confirmed through histological staining and examination. This transformation results in a mixed histological pattern, where areas of conventional RCC are interspersed with sarcomatoid components. These cells exhibit increased mitotic activity, pleomorphism, and atypia, contributing to the aggressive nature of the disease. Sarcomatoid differentiation in RCC is associated with a higher likelihood of metastasis compared to other RCC subtypes. The disease often spreads to distant organs, such as the lungs, liver, bones, and brain, at an early stage, complicating treatment efforts. One of the most significant challenges in managing sarcomatoid renal cell carcinoma is its resistance to established therapies. Conventional treatments, including surgery, targeted therapy, and immunotherapy, are often less effective in patients with sarcomatoid renal cell carcinoma, necessitating the exploration of new therapeutic approaches. Despite initial successful treatment, SRCC frequently recurs at a high rate, which is a significant factor contributing to its poor prognosis.

Case report

We report a case of a 55-year-old male who presented to the nephrology department with complaints of pain in the right lumbar region, hematuria, and burning micturition which emphasizes a complex renal pathology necessitating thorough evaluation and intervention. An ultrasound (USG) of the abdomen was conducted, it revealed an enlarged right kidney measuring13 x 4 cm. The USG also detected with a large heteroechoic mass in the mid and lower pole measuring 7 x 5 x 2 cm, along with a sub capsular hematoma in the upper pole. Due to these findings, a right nephrectomy was performed to remove the affected kidney. The resected specimen was subsequently sent for histopathological examination to determine the nature of the mass. Also, immunohistochemistry was carried out to confirm the diagnosis and further characterize the tumor. This case highlights the importance of extensive diagnostic approaches in managing complex renal conditions.

Gross examination

Upon gross examination of the nephrectomy specimen, which was received in formalin, the ureter was found to measure 7 cm in length, while the kidney measured 13 x 8 x 4.5 cm. The cut surface of the kidney revealed a well-circumscribed lesion measuring 7 x 5 x 2 cm, located predominantly in the middle pole and extending into the lower pole. Additionally, the upper pole of the kidney exhibited extensive areas of hemorrhage.

Microscopy

On microscopy, sections obtained from the tumor proper exhibit a histological pattern which is characterized by spindle-shaped tumor cells arranged in sheets, intersecting bundles, and fascicles. These cells display distinctive features, including plump vesicular nuclei with prominent nucleoli and a moderate amount of eosinophilic cytoplasm. Mitotic figures are clearly visible, indicating active cellular division. 1-2 mitosis per hpf were seen. Additionally, scattered regions within the specimen show sheets of round cells with clear cytoplasmic content.

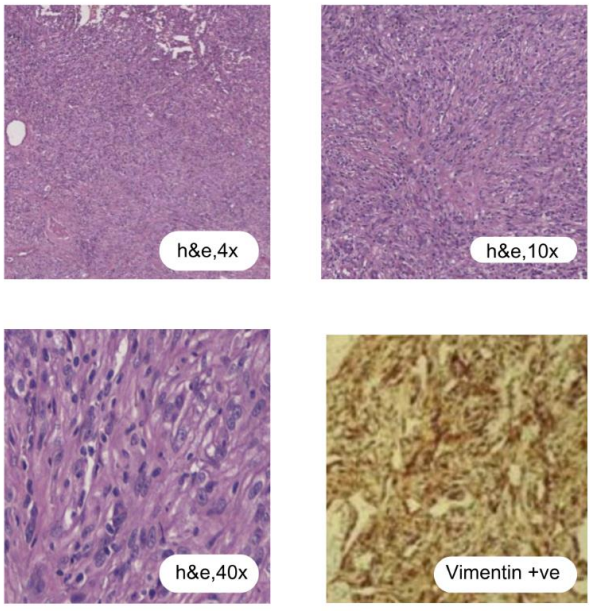

Fig 1. Histologic grade: Grade 2; Sarcomatoid features: Present; Tumor extent: Extends into the pelvicalyceal system, perinephric tissue, renal sinus and into the Gerota's fascia; Percentage of sarcomatoid element: 70%; Margin involved: Renal parenchyma, renal capsular area perinephric fat, renal sinus and Gerota's fascia; Lymph nodes: No lymph nodes were found; Primary tumor- pt4; Regional lymph node- pnx; Distant metastasis- pmx.

The stroma between these cellular arrangements appears sparse, with limited vascular structures observed. Furthermore, areas of necrosis and mild inflammatory infiltrates are present, contributing to the overall histopathological profile of the tumor specimen.

Immuno-histochemistry

Pan cytokeratin and pax8 were found to be diffusely positive. Moreover, immunohistochemical staining for vimentin shows cytoplasmic positivity specifically in the sarcomatous areas of the specimen.

Discussion

Renal cell carcinoma with sarcomatoid differentiation is an aggressive clinicopathological variant of RCC[1]. The overall incidence of sarcomatoid differentiation is 4% of all subtypes of RCC[2]. This differentiation can be seen in 5-8% of clear cell RCC, 8-9% of chromophobe RCC, and 2-3% of papillary RCC[3]. Hence RCC with sarcomatoid differentiation is not considered a distinct histological subtype of RCC due to its occurrence in all variants of RCC[2,3]. The conversion of primary tumor cells of RCC into sarcomatous occurs due to distinct driver mutations and clonal divergence during tumor progression[4]. These include increased expression of programmed death 1 (pd-1) and programmed death ligand-1 (pd-l1) compared to primary tumor cells[1,3]. These driver mutations lead to a process called epithelial-mesenchymal transition[3,5], in which the cells lose their epithelial markers such as e-cadherin[3,5] intensify the expression of mesenchymal markers such as snail[5] zeb, and twist[3], that play a key role in invasion and metastasis. The snail transcription factor plays a crucial role in this process[5]. Statistically significant associations have been found between increased snail expression and high fuhrman grade[5]. Studies indicate that these markers could be useful to evaluate the aggressiveness of lesions and to determine a better targeted therapy. The morphological changes that occur during epithelial mesenchymal transition include loss of cell polarity and cell to cell contact of epithelial cells, in order to attain a mesenchymal phenotype[5]. The sarcomatous nature of the tumor renders it prone to metastasis and enhances its resistance to already established systemic targeted therapies. Currently used treatment modalities include the use of gemcitabine[6,7], doxorubicin[6,7,8,9], ifosfamide[9], and their combinations which have reported a survival rate of around 20 to 60 months[3,6,7,8,9] after commencement of treatment. Due to the increased expression of pd-1 and pd-l1, the blockade at its axis may become an attractive therapeutic approach in the future[1,3]. Most studies have proven a poor median survival rate of 5 to 12 months and recurrence of the tumor following nephrectomy after 2 years[1]. Some studies have shown that even the presence of a 10% sarcomatoid element increases the risk of death by 6%[3].

In comparison to previous studies on renal cell carcinoma with sarcomatoid differentiation, the present study involves a slightly younger patient (55-year-old), in contrast to older median ages seen in studies of Cheville et al (2004)[2], Shuch et al (2012)[10], and the Libre Pathology case[11] where the median age of the patients ranged from 60 to 62 years. Most of these studies had common presenting symptoms such as hematuria, weight loss, and flank pain, unlike present study where the presenting symptoms were burning micturition and lumbar pain.

Table 1: Differences in the patients' ages and symptoms compared to earlier reports

Study and year of study	Median age	Gender	Presenting symptoms	Tumor characteristics	Mitosis and atypia
Cheville et al., 2004[2]	61	Male	Flank pain, hematuria, palpable mass	Common in clear cell RCC, large tumors	High mitotic rate, sarcomatoid areas extensive
Shuch et al., 2012[10]	60	Male	Fever, weight loss, fatigue, hematuria	High grade tumors, common sarcomatoid features	High mitotic activity, pleomorphic cells
Libre Pathology case[11]	60	Male	Gross hematuria, weight loss, fatigue	Often associated with clear cell RCC	High-grade atypia, numerous mitoses
Present report 2024	55	Male	Lumbar pain, hematuria, burning micturition	Spindle shaped tumor cells in clear cell RCC background	Spindle shaped cell, mitosis, sparse stroma

Tumor characteristics of the present study remain consistent with other studies, being linked with clear cell RCC background and characteristic spindle shaped cells. Mitosis was common in all of the given studies, with varied degrees of differentiation. However, spindle shaped cells in sparse stroma background was found in present study, in contrast to high mitotic activity with pleomorphic cells and extensive sarcomatoid areas seen in Shuch et al[10] and Cheville et al[2] in their studies respectively.

Overall, the present study stays consistent with the typical aggressive tumor patterns seen in RCC. However, there are some slight differences in the patients' ages and symptoms compared to earlier reports.

Conclusion

To conclude, we can say that the limited available information regarding sarcomatoid renal cell carcinomas (SRCCs) highlights the urgent requirement for continuous research into their biology, diagnostics, and treatment strategies. Conventional therapies have proven ineffective, leaving few viable options for individuals diagnosed with SRCC. The debate over cytoreductive nephrectomy for metastatic SRCC continues, with recent literature supporting surgical resection at any disease stage for patients with favorable performance status. The increased expression of pd1 and pdl1 in SRCCs compared to non-sarcomatoid RCCs has generated significant interest in exploring combinations of immune checkpoint blockade therapies with other systemic treatments, like ongoing clinical trials. Large-scale collaborative efforts are crucial to improving our understanding of SRCCs and developing more effective therapies for this aggressive form of cancer. Highlighting the importance of the detailed documentation of SRCC in pathology reports for optimum patient care and desirable outcomes.

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