

Case Study

Pathological features and immunohistochemical characteristics of clear cell (glycogen-rich) urothelial carcinoma: a case report and systematic review of the literature

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Abstract

Clear cell (glycogen-rich) urothelial carcinoma is an exceedingly rare variant of invasive urothelial carcinoma, distinguished by the presence of abundant cytoplasmic glycogen, which imparts a clear appearance to the tumor cells under histological examination. In this case report, the diagnosis was established through histopathological evaluation with hematoxylin and eosin (HE) staining, immunohistochemical analysis, and the identification of significant cytoplasmic glycogen accumulation. The patient, an 89-year-old male, was admitted on July 24, 2024, presenting with painless gross hematuria persisting for one week. Abdominal ultrasound and CT urography revealed a soft tissue mass on the right side of the bladder wall, measuring 30 × 30 mm, with a broad base connected to the bladder wall. The mass exhibited significant enhancement on contrast-enhanced scans, raising suspicion for malignancy. Microscopic examination revealed two distinct tumor cell morphologies: the conventional urothelial carcinoma pattern and a clear nest-like morphology, with the latter comprising over 70% of the tumor. Immunohistochemical staining for GATA-3, CK7, PAS, PAS-D, CAIX, PAX8, and RCC confirmed the diagnosis of clear cell (glycogen-rich) urothelial carcinoma. This rare variant of invasive urothelial carcinoma underscores the need for detailed diagnostic analysis to inform prognosis and treatment strategies. There have been similar cases reported before, involving a 57-year-old male-patient (Sahetia et al. in *Ind J Cancer* 60:575–577, 2023).

Keywords Clear cell · Urothelial carcinoma · Rare · PAS staining

1 Introduction

According to the 2022 WHO classification of urothelial tumors [2], clear cell (glycogen-rich) urothelial carcinoma is categorized as a variant of invasive urothelial carcinoma. This variant is characterized by a high glycogen content within the cytoplasm, which imparts a clear appearance to the tumor cells, resembling that of clear cell renal carcinoma. While the prognosis of various invasive urothelial carcinoma variant, such as sarcomatoid urothelial carcinoma—with a five-year survival rate of less than 20% [3]—is well-documented, the prognosis for clear cell (glycogen-rich) urothelial carcinoma remains uncertain. Accurate diagnosis and further investigation are essential to better understand the prognosis and develop targeted treatment options for this rare variant.

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2 Case report

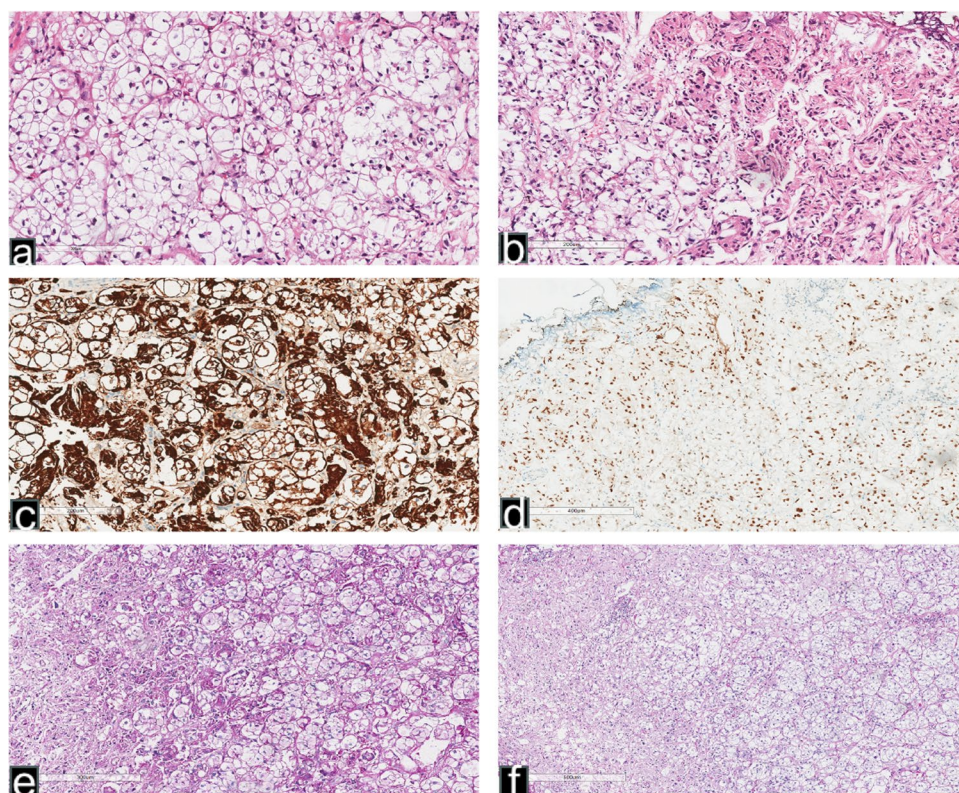
The patient, an 89-year-old male, presented with a one-week history of painless gross hematuria and was admitted to the hospital on July 24, 2024. Upon admission, comprehensive diagnostic evaluations, including abdominal ultrasound and CT urography, were conducted. Imaging revealed a soft tissue mass measuring 30 × 30 mm on the right side of the bladder wall, with a broad base of attachment and significant enhancement on contrast-enhanced scans, indicating a high likelihood of malignancy. Additional findings included multiple cystic lesions in both kidneys, with the largest cyst measuring approximately 70 × 53 mm, exhibiting well-defined margins and no significant enhancement. The prostate also demonstrated localized uneven enhancement. Given the clinical findings, further diagnostic procedures were undertaken, and a tissue biopsy was obtained for histopathological examination.

The specimen comprised a pile of gray-white and gray-red tissue, measuring 1.4 × 0.7 cm, with a fragile texture. Microscopically, the majority of the tumor exhibited clear nest-like structures with abundant capillaries between the nests, reminiscent of renal clear cell carcinoma. The tumor cells displayed clear cytoplasm, with most nuclei centrally located, although some showed nuclear displacement. The nuclei exhibited mild atypia, being large with distinct nucleoli (Figure 1a). In addition to the clear cell nests, areas of typical invasive urothelial carcinoma were observed, characterized by an increased nuclear-to-cytoplasmic ratio, marked nuclear atypia, and reduced cell adhesion, with tumor cells infiltrating the bladder muscle layer as nests or single cells (Figure 1b). The clear cell nests constituted more than 70% of the entire tumor.

Subsequently, immunohistochemical staining was performed on the tumor tissue. The results revealed that CK7 (Figure 1c), P63, and GATA-3 (Figure 1d) were positively stained in both the clear cell nests and the classic invasive urothelial carcinoma areas. CD10 was positively stained in the clear cell nests, while CK20 was positively stained in the classic areas and negatively in the clear cell nests. RCC, PAX-8, CAIX, and PSA were all negative in both the clear cell nests and the classic invasive urothelial carcinoma. To verify the presence of glycogen in the cytoplasm of the clear cells, special staining with PAS (Figure 1e) and PAS-D (Figure 1f) was conducted. The PAS staining showed the presence of glycogen granules in the cytoplasm of the tumor cells, while PAS-D staining did not, confirming that the clear tumor cells contained glycogen.

Based on the diagnostic criteria, the patient was accurately diagnosed with clear cell (glycogen-rich) urothelial carcinoma.

Fig. 1 **a** HE 200 ×: Section shows clear tumor cells arranged in a nest-like pattern. **b** HE 200 ×: Section shows muscle-invasive tumor of classical bladder cancer and clear tumor cells (The left side is the clear cell area, and the right side is the classic area). **c** CK7 200 ×: CK7 highlights the clear tumor cells and classical bladder cancer. **d** GATA-3 200 ×: GATA-3 highlights the clear tumor cells and classical bladder cancer. **e** PAS 400 ×: Glycogen staining is positive in clear tumor cells and classical bladder cancer. **f** PAS-D 400 ×: Glycogen staining is negative in clear tumor cells, glycogen staining is positive in classical bladder cancer. HE hematoxylin and eosin, PAS periodic acid–Schiff, PAS-D periodic acid–Schiff with diastase



3 Discussion

Invasive urothelial carcinomas are often aggressive, with many variants associated with poor prognoses [3]. In 1995, Kotliar et al. [4] reported on 17 patients with clear cell variants of urothelial carcinoma and were the first to describe the proportion of clear tumor cells independently. Among these 17 cases, the proportion of male patients was greater than that of female patients (approximately 12:5), with patient ages ranging from 55 to 82 years and a median age of 71.5 years. The patient reported in this case was 89 years old. Most patients are diagnosed with painless gross hematuria [5], and this case was no exception.

Since the clear cell nests in this case account for more than 70% of the tumor, it is necessary to differentiate it from other clear cell metastatic cancers. After further examination, the patient was found to have multiple cystic lesions in the left kidney, the largest of which measured approximately 70 × 53 mm. Since these renal cystic lesions were not subjected to pathological examination, there remained a possibility of renal clear cell carcinoma with metastasis to the bladder. Therefore, a differential diagnosis was warranted. Immunohistochemistry for renal clear cell carcinoma was performed, with results showing negative staining for RCC, CAIX and PAX-8. Additionally, the multiple cystic lesions in the kidney exhibited minimal solid components, further reducing the likelihood of renal clear cell carcinoma.

In the HE sections, some cells appeared slightly eosinophilic and clear, with slightly prominent cell membranes and positive CK7 immunohistochemistry, leading to a consideration of renal chromophobe cell carcinoma. However, differential diagnosis was pursued. The clear tumor nests expressed urothelial markers such as GATA-3 and P63, supporting their urothelial origin. Moreover, chromophobe renal cell carcinoma typically exhibits minimal nuclear atypia with inconspicuous nucleoli, which did not match the features observed in this case, thus ruling out this possibility. PSA staining was also conducted to rule out prostate cancer.

A review of the literature [6] indicates that clear cells of urothelial carcinoma, rich in glycogen, have glycogen-containing cytoplasm. To confirm this, special staining with PAS and PAS-D was performed. The PAS staining showed glycogen granules in the cytoplasm of the tumor cells, while PAS-D staining did not, confirming the presence of glycogen in the cytoplasm of the clear tumor cells. Some studies suggest that abundant glycogen in the cytoplasm may correlate with higher malignancy [1]. The results of this experiment demonstrate that in the same patient, the PAS-D staining of the clear cell area is transparent, indicating that the clear cell area is rich in glycogen, while the classic area does not exhibit this phenomenon. Other studies have shown that the survival rate of patients with clear cell carcinoma who have undergone surgery and chemotherapy ranges from 14 weeks to 24 months [5]. However, due to the rarity of this tumor and the lack of standardized treatment protocols, the prognosis remains uncertain.

4 Conclusion

Clear cell (glycogen-rich) urothelial carcinoma is a rare variant of invasive urothelial carcinoma, and its biological behavior is not yet fully understood. Based on survival rate surveys, I speculate Clear cell (glycogen-rich) urothelial carcinoma may predict a poorer prognosis compared to the conventional type of urothelial carcinoma. Moving forward, I will continue to follow up with this patient and summarize the survival rates of similar cases.

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Author contributions Weiming Wang wrote the manuscript, Baogang Zhang, Zhangli Wu, Chuanling Hou participated in the pathological examination, and Mengyao Li, Tianyi Zhang collected the data. All authors have read and agreed to the final manuscript.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate This study was conducted retrospectively from data obtained for clinical purposes. Ethical approval has been exempted by the Ethics Committee of Shaoxing People's Hospital. This study was conducted in accordance with local regulations and the ethical standards stipulated in the 1964 Helsinki Declaration.

Consent for publication Informed consent to participate in and publish the study was obtained from participants (or their parents or legal guardians in the case of children under 16).

Competing interests The authors declare no competing interests.

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