Adrenal cyst misdiagnosed with cystic renal cell carcinoma: A case report

XIN HUANG[1], MENGYU ZHANG[2], YIJUN ZHAN[3], CE CHEN[2], XINHUA ZHANG[4] and YAOZHONG XU[2]

[1]Operating Room, People's Hospital of Tuanfeng, Huanggang, Hubei 438000, P.R. China; [2]Department of Urology, People's Hospital of Tuanfeng, Huanggang, Hubei 438000, P.R. China; [3]Department of Pathology, People's Hospital of Tuanfeng, Huanggang, Hubei 438000, P.R. China; [4]Department of Urology, Zhongnan Hospital of Wuhan University, Wuhan, Hubei 430071, P.R. China

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Abstract. Adrenal cysts are rare adrenal masses that are typically benign and are often incidentally discovered during imaging examinations. However, their complex imaging characteristics can lead to misdiagnosis, particularly when they closely adhere to the upper pole of the kidney, thus resembling renal cysts or cystic renal cell carcinoma (RCC). The present study describes the case of a 41-year-old male patient who presented with left flank pain and was initially diagnosed with a left renal cyst. Imaging examinations identified a simple renal cyst at the upper pole of the left kidney closely adhering to the left adrenal gland. The patient underwent posterior retroperitoneoscopic left renal cyst decortication and subsequent histopathological examination revealed clear cells lining the cyst wall, indicative of low-grade clear cell RCC. Due to the discrepancy between the clinical and radiological findings and the pathology report, a multidisciplinary team was convened. An expert pathological consultation was recommended, which resulted in a revised diagnosis of an adrenal cyst. The present study highlights the diagnostic challenges in distinguishing adrenal cysts from renal cysts and RCC by imaging and histopathology. The present study also underscores the need for multidisciplinary collaboration and thorough pathological evaluation, including the use of appropriate immunohistochemical staining, to avoid misdiagnosis.

Introduction

Adrenal cysts are rare lesions, with an incidence of 0.06-0.18% in autopsies (1), accounting for 1-2% of all adrenal incidentalomas (2,3). These cysts are commonly benign and non-functional, with the majority of cases being incidentally identified during imaging examinations performed for unrelated reasons (2-4). Adrenal pseudocysts, the most common subtype, likely evolve from prior intraglandular hemorrhage triggered by anticoagulation, trauma, coagulopathy, pregnancy or underlying neoplasia, whereas endothelial cysts are thought to derive from vascular or lymphatic malformations and parasitic cysts arise almost exclusively in endemic regions after exposure to parasitic infections (such as *Echinococcus*) (3,5). Only 10% of all patients with adrenal cyst present with symptoms (3,5). The majority of adrenal cysts are asymptomatic and slow-growing, with a slight predominance in women and a common age of diagnosis between 40 and 60 years (3). Current evidence supports conservative management for small, asymptomatic, non-functional lesions. However, surgical intervention (such as laparoscopic adrenalectomy or selective cystectomy) is recommended for growing, symptomatic or hormonally active cysts after multidisciplinary review (3,6-8). Adrenal cysts can occasionally be indistinguishable from benign renal cysts located at the upper pole of the kidney and the cystic transformation of renal cancer, thus increasing the risk of misdiagnosis.The present study reports the case of a patient with an adrenal cyst, which was initially misdiagnosed as cystic renal cell carcinoma (RCC), and outlines the diagnostic and treatment approaches applied at the People's Hospital of Tuanfeng (Huanggang, China). Furthermore, the clinical, imaging and pathological characteristics of adrenal cysts reported in the literature were reviewed, thus highlighting the diagnostic challenges in differentiating adrenal cysts from renal cysts and cystic RCC. In the present study, comprehensive literature searches in both the PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (https://www.webofscience.com) databases were performed. The search identified only 1 reported case of adrenal cyst misdiagnosed as RCC (9), and no documented cases of adrenal cysts being misdiagnosed as cystic RCC to date. The detailed search strategy is provided in Table SI.

Case report

The present study reports the case of a 41-year-old male patient with left flank pain for >3 days. The patient had been diagnosed with a left renal cyst and left renal calculi via ultrasound at another hospital 2 years ago. Upon admission to the People's

Correspondence to: Dr Yaozhong Xu, Department of Urology, People's Hospital of Tuanfeng, 15 Square Road, Tuanfeng, Huanggang, Hubei 438000, P.R. China
E-mail: bein81@126.com

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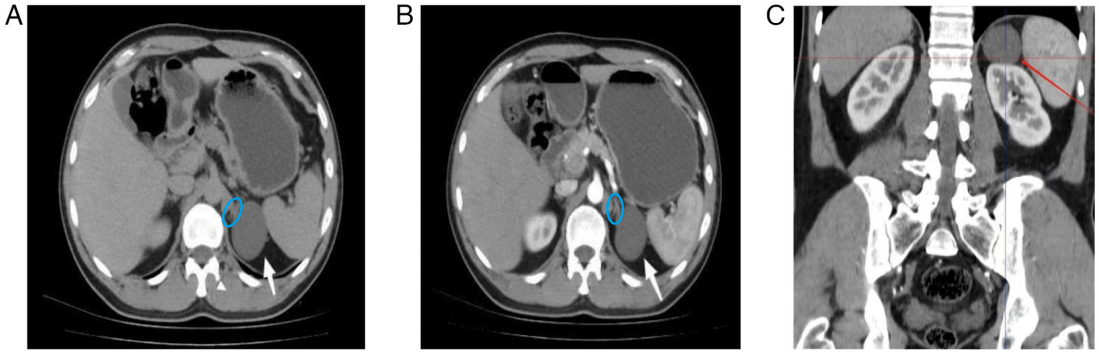

Figure 1. Plain and contrast-enhanced CT images of the adrenal cyst. (A) Plain CT scan showing a low-density, round mass at the junction of the left adrenal gland. The white arrow indicates the cyst. The blue oval outlines the left adrenal gland. (B) Contrast-enhanced CT during the arterial phase showing no enhancement of the cyst. The white arrow indicates the cyst. The blue oval outlines the left adrenal gland (inverted-Y shape). (C) Coronary CT reconstruction during the arterial phase showing the cyst. The red arrow indicates the adrenal cyst located at the upper pole of the left kidney.

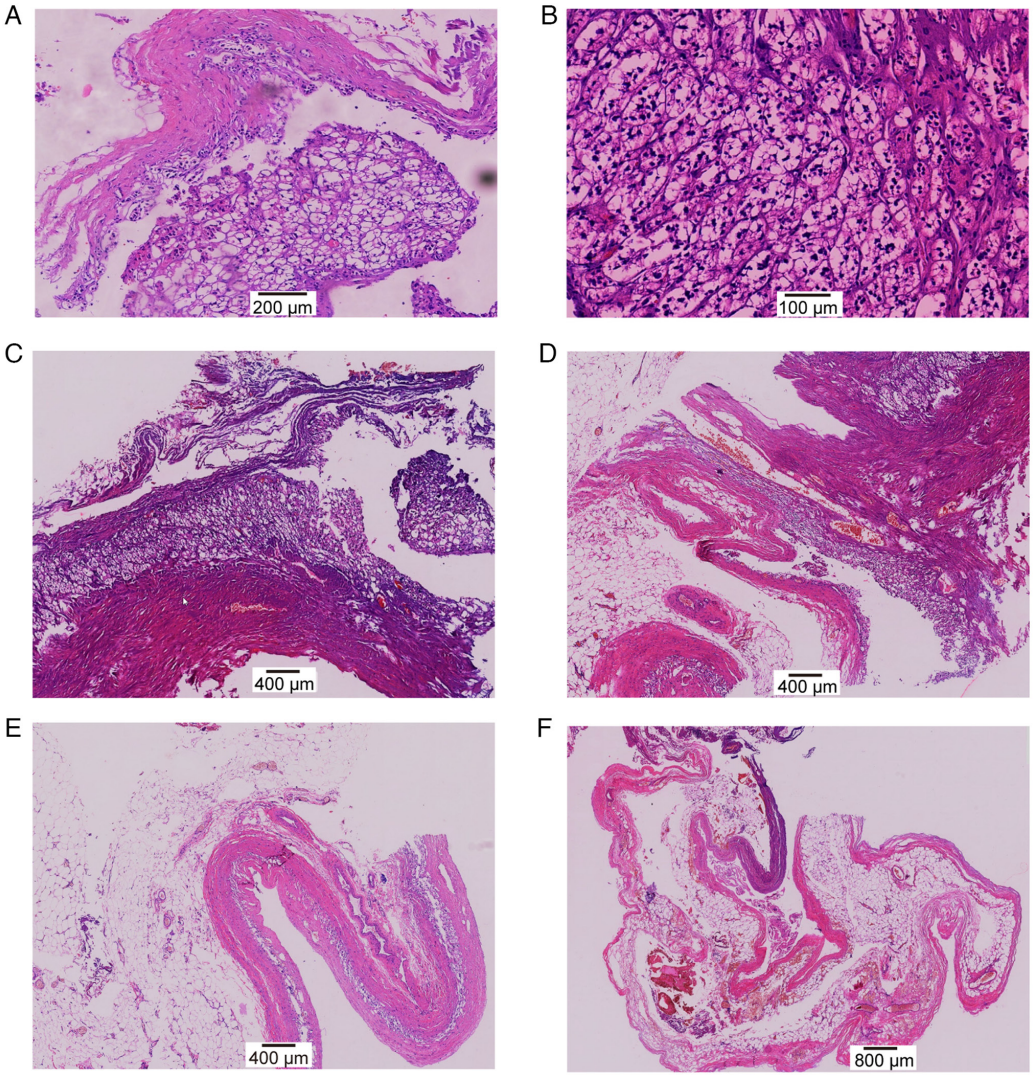

Figure 2. H&E staining of the adrenal cyst. (A) Irregular clear cells lining the cyst wall are shown (magnification, x100). (B) Clear cytoplasmic features of cells within the cyst wall (magnification, x200). (C) Overview of the entire cystic structure (magnification, x40). (D) Cyst containing erythrocytes with clear cells in the cyst wall is shown (magnification, x40). (E) Fibrous tissue hyperplasia is observed in the cyst wall (magnification, x40). (F) Fibrofatty tissue surrounding the cyst (magnification, x20).

Hospital of Tuanfeng in December 2023, a plain and contrast-enhanced CT scan of both kidneys was performed, revealing a simple renal cyst, ~5 cm in diameter, located at the upper pole of the left kidney. The cyst was closely adherent to the left adrenal gland and was classified as a Bosniak classification (10) Grade I (Fig. 1). No other notable abnormalities were recorded

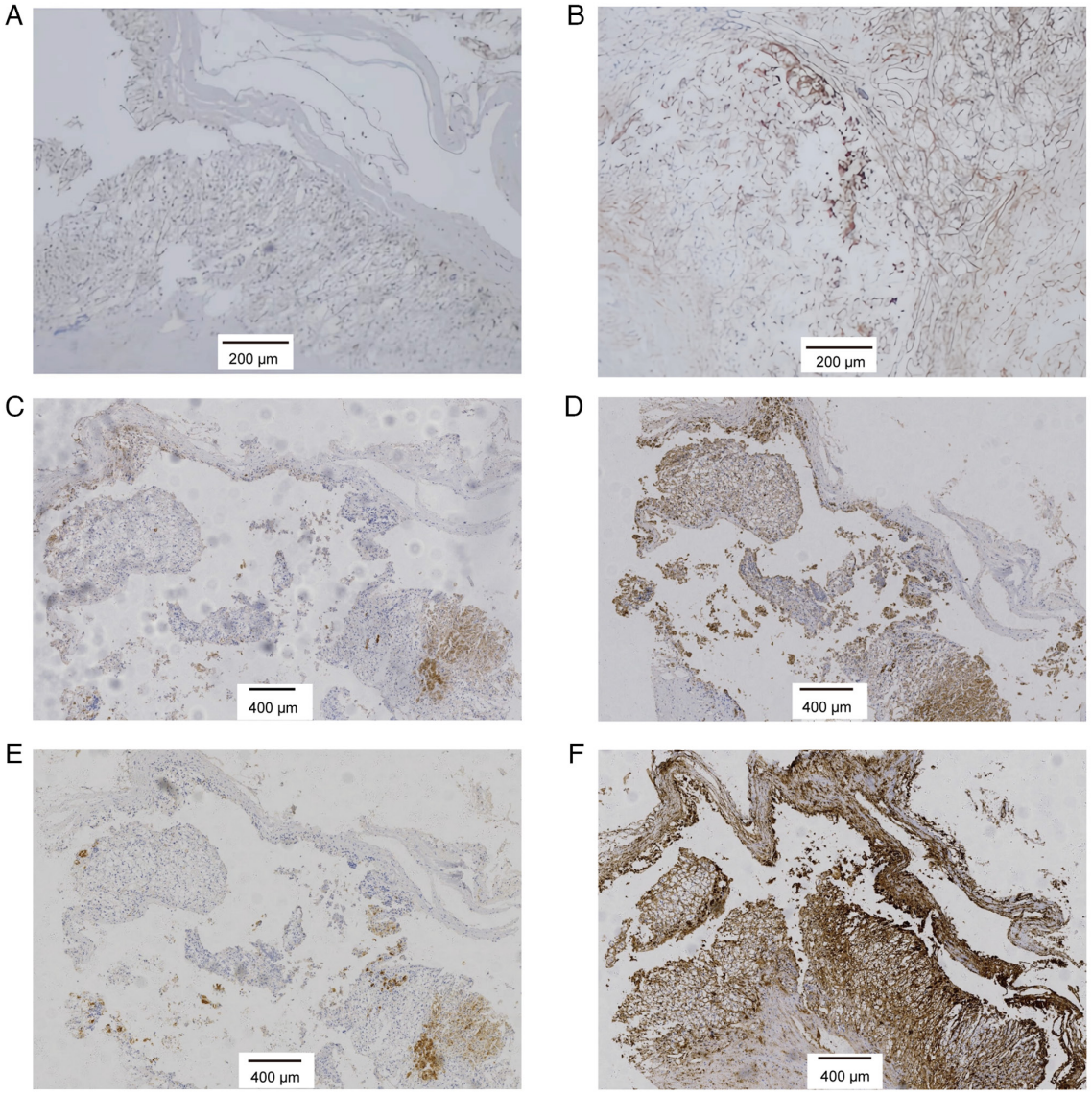

Figure 3. Immunohistochemical staining of the adrenal cyst. (A) Cluster of differentiation 10-positive (magnification, x100), (B) vimentin-positive (magnification, x100), (C) inhibin-α-positive (magnification, x40), (D) melan-A-positive (magnification, x40), (E) synaptophysin-positive (magnification, x40), and (F) vimentin-positive (magnification, x40) staining are shown. The panels (A and B) represent the first immunohistochemical stains, while (C-F) show the additional immunohistochemical analysis.

in the remaining examinations (including complete blood count, urinalysis, comprehensive metabolic panel and coagulation tests). The patient was anxious about the cyst and experienced left flank pain. After excluding surgical contraindications, posterior retroperitoneoscopic left renal cyst decortication under general anesthesia was performed (11). During surgery, despite careful dissection, it was not possible to determine whether the cyst originated from the kidney or the adrenal gland.

The surgically resected cyst tissue specimens were fixed in 10% neutral buffered formalin at room temperature within 30 min after resection for ~20 h. After complete sampling, dehydration (gradient ethanol) was performed, followed by paraffin embedding to create wax blocks. Sections were cut at a thickness of 3 µm. Permeabilization was performed with 5 mM EDTA retrieval solution, pH 9.0, at 100˚C for 20 min. Endogenous peroxidase activity was quenched by incubation with 3% hydrogen peroxide for 5 min at room temperature. All primary antibodies were incubated at room temperature. The primary antibody information is summarized in Table SII. The secondary antibodies were conjugated to an HRP-polymer complex, which binds to the primary antibodies to form a detectable signal. All secondary antibodies used in the present study were the undiluted ready-to-use Bond Polymer Refine Detection kit (cat no. DS9800; Leica Biosystems) or the EnVision FLEX+, Mouse, High pH (Link) kit (cat. no. K8002; Agilent Technologies, Inc.) and were incubated with the samples for 8 (Leica) or 20 (Agilent) min at room temperature. For chromogenic detection, 3,3'-diaminobenzidine (DAB) was prepared by mixing DAB substrate with DAB buffer at a 1:20 ratio, which was incubated with the sample for 10 min at room temperature. For counterstaining, the sections were washed with purified water, followed by the addition of 100 µl hematoxylin staining solution for 3-5 min. The sections were then washed with purified water for bluing. The microscope used for the specimens was an optical microscope (Olympus CX31; magnification, 40-400x). Neutral balsam was used as

the mounting medium. Digital slide scanning and analysis were carried out using the PRECICE® 610 Digital Slide Scanning and Analysis System (Youyun Intelligent Technology Co., Ltd.).

Histopathological examination revealed irregularly shaped clear cells lining the cyst wall (Fig. 2), which suggested cystic involvement with clear cell RCC. Immunohistochemical (IHC) staining indicated the following profile: Cytokeratin 7 (-), α-methylacyl-CoA racemase (-), cluster of differentiation (CD)117 (-), epithelial membrane antigen (-), carbonic anhydrase IX (-), CD68 (-), Ki-67 (<1%), CD10 (+) and vimentin (+) (Fig. 3A and B). This combination, particularly CD10 and vimentin positivity with low proliferation, closely resembles the typical immunophenotype of low-grade clear cell RCC. Based on the initial diagnosis of clear cell RCC, radical nephrectomy was scheduled. However, during preoperative planning, discrepancies between the radiological and clinical findings raised concerns regarding the pathological diagnosis, which prompted a multidisciplinary team (MDT) consultation. The MDT recommended expert pathological consultation and additional IHC staining analysis was carried out, which revealed positivity for inhibin-α, melan-A, synaptophysin and vimentin (Fig. 3C-F). The established scoring criteria for immunohistochemical staining intensity are provided in Table SIII. Based on the aforementioned findings, the final diagnosis was revised to adrenal cyst, thus avoiding the need for radical nephrectomy. After a 1-year follow-up (December 2024), no recurrence of the adrenal cyst was observed in the patient.

Discussion

Benign adrenal cysts typically appear as well-demarcated, commonly rounded masses with thin walls and homogeneous internal structures. On imaging, they present with low attenuation on CT, low signal on T1-weighted MRI images and with high signal on T2-weighted sequences (12,13). Due to the anatomical location of the lesion, the imaging manifestations of adrenal cysts are complex and variable, which makes their differentiation from renal cysts and abdominal lymphangiomas occasionally difficult (3,5,14). Renal or pancreatic cysts can also invade the adrenal gland. Multiplanar CT/MRI scans serve a key role in determining the origin of the lesion. For example, renal cysts typically arise within the contour of the kidney, while pancreatic pseudocysts are associated with peripancreatic inflammation and a history of pancreatitis (3,13). In the present case report, the left adrenal cyst was closely adherent to the upper pole of the left kidney, thus compressing the kidney. However, the origin of the cyst could not be distinguished by preoperative CT. Therefore, a cyst decortication was performed. Furthermore, the intraoperative findings of close adhesion to the left adrenal gland suggested that the cystic mass arose from the adrenal gland. The aforementioned observation highlighted the importance of re-evaluating the preoperative diagnosis and considering a broader intraoperative dissection to verify the origin of the mass. Based on the present case, the following measures are recommended for similar cases in the future: i) High-resolution MRI should be performed to further localize the cyst and determine whether it originates from the kidney, adrenal gland or another organ; ii) preoperative MDT discussions should be also conducted to establish the most appropriate treatment plan, in accordance with the current European Society of Endocrinology clinical practice guidelines (7); and iii) a larger area should be intraoperatively dissected to accurately assess the origin of the cyst.

Histologically, adrenal cysts are categorized into pseudocysts and endothelial, epithelial and parasitic cysts. Among them, pseudocysts are the most common surgical cases, accounting for ~80% of all cases, and often result from encapsulated adrenal hemorrhage (3,15). Endothelial cysts, the most frequent type in autopsy series (~45%) (4), are lined by a monolayer of endothelial cells, while epithelial cysts have a thin capsule lined by flat-to-cuboidal cells (3,16). Pathologically, adrenal cysts often need to be differentiated from cystic pheochromocytoma (3). The key feature of the pathological classification of adrenal cysts is the structure of the cyst wall. The cyst wall of a pseudocyst is composed of fibrous tissue containing fibrin hemorrhagic fluid without an internal cellular structure. Furthermore, endothelial (vascular) cysts originate from dilated and thrombosed blood vessels or lymphatics and are composed of a single layer of flat endothelial cells. Epithelial (mesothelial) cysts have commonly thin wells, associated with mesothelial remnants and are composed of flat and cuboidal mesothelial cells arranged side by side. Lastly, parasitic cysts, most frequently associated with echinococcosis, can contain parasites within the inner wall (3,5). These cysts, which are often surrounded by fibrous calcified cyst walls, can be composed of a single or multiple cavities, supplemented with a transparent fluid (3,5).

In the present case report, the initial pathological diagnosis was inconsistent with the preoperative CT scan and intraoperative findings, and therefore an MDT discussion was initiated. After the urologists, oncologists, radiologists and pathologists reviewed the case, it was concluded that the clinical, radiological and pathological findings were inconsistent. Based on the aforementioned discrepancy, the pathologists were recommended to consult with senior reference pathologists. Finally, pathological assessment combined with IHC verified that the lesion was an adrenal cyst.

Regarding the reasons for misdiagnosis in the present case, the following contributing factors were identified. Firstly, there was insufficient communication between the surgical and pathological teams. The resected tissue sample was not thoroughly described in terms of its specific location and was generally designated as a 'renal cyst.' Secondly, adrenal metastases from clear cell RCC, often cystic and with high lipid content, can be misdiagnosed on chemical-shift MRI imaging (17). A fibrous adrenal cyst can sometimes fuse with the renal capsule, leading to notable challenges for pathological differentiation from primary renal cystic lesions (18). In the present case, the pathologist misinterpreted the lipid cells of the adrenal tissue as clear cells characteristic of clear cell RCC, thus leading to a misdiagnosis. Furthermore, the nuclei in this specimen were poorly defined, thus hindering accurate differentiation. Thirdly, the IHC antibodies used in the present case were not selected based on the type of adrenal tumor, thus resulting in non-specific and inconclusive results. This further contributed to pathological misdiagnosis. Therefore, to accurately differentiate cystic lesions from tumors, the following primary antibodies should be used: Vimentin, pancytokeratin, melan-A, inhibin-α, synaptophysin, chromogranin A, paired box gene 8 and carbonic anhydrase IX (19,20).

The outcome of the present case report suggests that surgeons should not solely rely on the 'authority' of pathological diagnosis. In cases where uncertainty exists, a thorough differential diagnosis should also be performed to reach a definitive conclusion. Notably, IHC reactions are indeed highly susceptible to the physicochemical conditions of the tissue samples. Engel and Moore (21) indicated that key variables, such as fixation methods, pH levels and temperature could markedly affect the accuracy of IHC results. For example, the choice of the fixative and its pH can greatly affect antigen preservation, while the temperature during tissue processing, such as during dehydration and fixation, can also affect the distribution and intensity of immunostaining. Additionally, the duration of fixation is also key and therefore both under- and over-fixation can lead to suboptimal staining outcomes (21-23). Furthermore, heat-induced epitope retrieval methods, such as microwave or pressure cooker techniques, are often employed to reverse formalin-induced cross-linking. However, excessive heat or improper buffer pH can damage epitopes (21). Therefore, the physicochemical milieu of the tissue samples, from fixation to storage, should be meticulously standardized to ensure accurate and reliable IHC results.

Given the rarity of both adrenal cysts and cystic RCC, the misdiagnosis of an adrenal cyst as cystic RCC is extremely rare. The limitations of the present case report were associated with the experience of the urological surgeon and particularly with the accuracy of the pathological diagnosis. Furthermore, MRI was not performed. During preoperative evaluation, the need to differentiate between a renal cyst and an adrenal cyst was not considered, therefore the urological CT scan was assumed to be sufficient for diagnosis. Not performing MRI is also one of the lessons learned from this case.

In summary, the present case report may provide the following three implications for urologists: i) This case highlights the diagnostic pitfalls among renal cysts, adrenal cysts and cystic RCC, underscoring the need for clinicians to maintain a broad differential diagnosis and to complete all relevant preoperative investigations; ii) adrenal cysts and cystic RCC share similar pathological features, and therefore pathologists should be vigilant to avoid misdiagnosis. The accurate diagnosis requires careful consideration of all clinical findings, the use of appropriate IHC markers and participation in clinical pathological MDT discussions, to ensure the correct pathological diagnosis; and iii) urologists should not rely solely on the conclusions drawn by radiologists and pathologists. When inconsistencies arise during the treatment process, the timely initiation of MDT discussions could promote diagnostic accuracy, thus establishing the most appropriate treatment strategy for patients with adrenal cysts in the future.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YX, XZ, MZ and CC performed the surgical procedure. YX, XH and XZ conceived and designed the study. YZ performed the histopathological examination. XH, MZ, YZ and CC wrote the manuscript. YX and XZ revised the manuscript. YX, MZ, YZ and XZ confirmed the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present case report was approved by the Ethics Committee of the People's Hospital of Tuanfeng (Huanggang, China; approval no. 20240014). Written informed consent was obtained from the patient.

Patient consent for publication

The patient provided written informed consent for the publication of the present case report.

Competing interests

The authors declare that they have no competing interests.

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