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Clinicopathological Analysis of Succinate Dehydrogenase-Deficient Renal Cell Carcinoma

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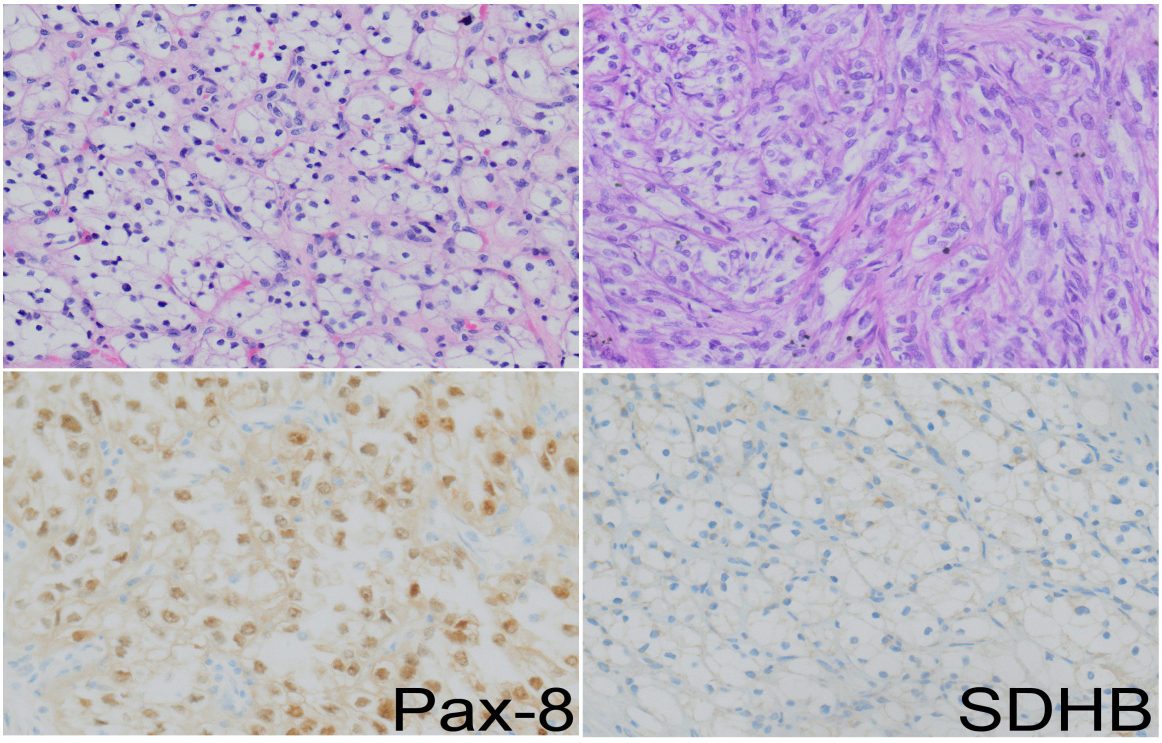
Graphical Abstract



This study analyzed the clinicopathological and molecular characteristics of 14cases of succinate dehydrogenase-deficient renal cell carcinoma (SDH-RCC),among which 4 cases were high nuclear grade. The results revealed the typicalhistopathological and immunohistochemical features of SDH-RCC, furtherenriched the case database of SDH-RCC, and provided a certain pathologicalbasis for subsequent research on SDH-RCC.

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Clinicopathological Analysis of Succinate Dehydrogenase-Deficient Renal Cell Carcinoma

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Abstract

Objective: To investigate the clinicopathological features, immunophenotype, key diagnostic points and prognosis of succinate dehydrogenase (SDH)-deficient renal cell carcinoma in order to provide a reference for its clinical diagnosis, treatment and pathological diagnosis.
Materials and Methods: The retrospective analysis was performed on 14 cases of SDH-deficient renal cell carcinoma, with a summary and evaluation of their clinicopathological, morphological, immunohistochemical features and prognosis.
Results: Among the 14 patients, 10 were male and 4 were female. The age ranged from 43 to 78 years, with a median age of 52 years. 9 tumors were located in the left kidney and 5 in the right kidney. Tumor size ranged from 1.5 cm to 8.0 cm. Microscopically, the tumor cells exhibited diverse architectural patterns, including predominantly solid and nested growth, occasional microcystic and cystiic dilatation, and papillary architecture. The tumor cells had abundant cytoplasm, which was vacuolated or weakly eosinophilic. Immunohistochemical results showed that all 14 tumor cells were positive for vimentin and PAX-8, and negative for SDHB, CK7, CD117, and CA IX. The Ki-67 proliferation index ranged from 5% to 20%. Among the 14 patients, 1 was lost to follow-up, and 13 were followed up. Of the 13 followed patients, 12 were alive and 1 died.
Conclusion: SDH-deficient renal cell carcinoma is a relatively rare subtype of renal cell carcinoma. Patients with low nuclear grade are generally younger, whereas those with high nuclear grade are mostly middle-aged or elderly and prone to metastasis. Loss of SDHB expression by immunohistochemical staining is helpful for the diagnosis of this type of tumor.
Keywords: Succinate dehydrogenase-deficient renal cell carcinoma; Histology; Immunohistochemistry; Diagnosis; Prognosis

Introduction

Succinate dehydrogenase (SDH) is a respiratory enzyme complex composed of four protein subunits, SDHA, SDHB, SDHC, and SDHD, and is localized to the inner mitochondrial membrane [1]. Its primary function is to catalyze the conversion of succinate to fumarate and facilitate electron transport in the respiratory chain [2]. SDH-deficient renal cell carcinoma (SDH-RCC) is a relatively rare subtype of RCC, which was first identified in 2004. It was officially classified as an independent subtype of RCC by the World Health Organization (WHO) in 2016. In 2022, it was formally defined as RCC with loss of SDHB expression and recognized as a distinct subtype of RCC [3-4].
As a rare subtype of RCC (accounting for 0.05%-0.2% of all RCC), SDH-RCC has been relatively uncommon reported in China, with limited relevant research available. Consequently, clinicians and pathologists lack sufficient familiarity with this entity, leading to a high risk of misdiagnosis. To improve the understanding of this subtype of RCC, we collected a total of 14 cases of SDH-RCC and summarized their clinicopathological and immunohistochemical features.

Materials and Methods

Case Collection

A total of 14 cases of SDH-RCC diagnosed between 2018 and 2024 were collected from the First and Second Affiliated Hospitals of Anhui Medical University, all of which met the diagnostic criteria for SDH-RCC. Detailed clinicopathological data and follow-up information were collected for each case. All histological slides were independently reviewed in a blind manner by two senior pathologists, and the microscopic pathological features of each specimen were documented in detail.

HE Staining and Immunohistochemical Staining

All specimens were obtained via surgical operation, including radical nephrectomy and partial nephrectomy. The specimens

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were fixed in formalin, embedded in paraffin, and subjected to routine deparaffinization and rehydration prior to HE staining. Histomorphological features were examined under a light microscope. Immunohistochemical staining was performed using the EnVision two-step method. The primary antibodies included SDHB (MXB Biotechnologies, clone 21A11AE7), vimentin (MXB Biotechnologies, clone MX034), PAX-8 (MXB Biotechnologies, clone EP298), CK7 (MXB Biotechnologies, clone OV-TL12/30), CD117 (MXB Biotechnologies, clone YR145), CA IX (MXB Biotechnologies, rabbit polyclonal antibody), and Ki-67 (Roche, clone 30-9).

Follow-Up

Follow-up information was collected through medical record review and telephone follow-up. The recorded parameters included tumor recurrence, metastasis, and patient survival status.

Result

Clinical Information

Detailed clinical information of the 14 patients was summarized (Table 1). The patients ranged in age from 43 to 78 years, with the mean age of 54.4 years and the median age of 52 years. Regarding gender, there were 10 males and 4 females, with a marked male predominance and a male-to-female ratio of 2.5:1. With respect to tumor location, 9 tumors were located in the left kidney and 5 in the right kidney. As for the reasons for initial presentation, 8 patients were asymptomatic and detected incidentally during physical examination, while the remaining patients presented with varying degrees of discomfort, including ipsilateral abdominal pain, lumbodorsal pain, abnormal liver function, and ipsilateral inguinal hernia. All patients underwent abdominal CT or MRI, which revealed a space-occupying lesion in the affected kidney (Figures 1A and 1B).

Gross Findings

The maximum tumor diameter ranged from 1.5 cm to 8.0 cm in the 14 patients. Among them, 9 tumors were obtained from partial nephrectomy specimens, and 5 from radical nephrectomy specimens of the affected kidneys.

The cut surfaces of the tumors exhibited variable colors, predominantly gray-white, gray-yellow, and gray-brown. Regarding tumor texture, cases 1, 4, 9, 11 displayed a cystic-solid cut surface, and the remaining cases showed solid and slightly firm cut surfaces. Most tumors were well-demarcated with pushing growth borders. Only cases 3, 13, and 14 showed invasion of the renal capsule and perirenal adipose tissue.

Histologic Features

Most tumors were well-circumscribed, with pushing borders into adjacent tissue and formation of a fibrous capsule. Focally, a lobular architecture was noted. Invasion into surrounding adipose tissue was identified in 3 cases. Entrapped non-neoplastic renal tubules were visible at the periphery of the tumors.

Tumor cells were arranged in solid sheets, nests, and tubules (Figures 2A, 2B), with prominent sinusoidal vasculature within tumor nests. Microcystic or multicystic structures were present in some cases (Figure 2C). In addition, focal micropapillary architecture was observed in 1 case (case 13; Figure 2D), and papillary structures were identified in 1 case (case 14; Figure 2E).

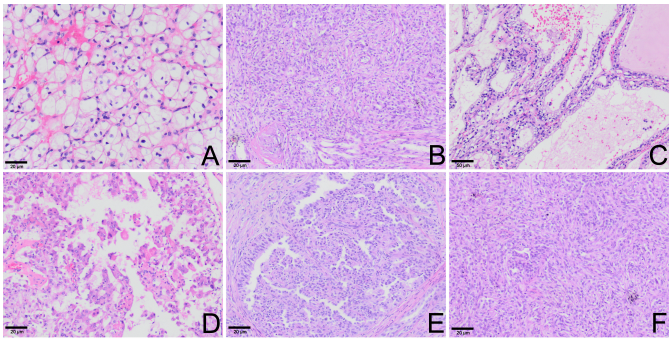

Figure 2. Histological features of SDH-RCC. (**A**) (**B**) Tumor cells are arranged in solid sheets, nests, and tubules (HE×400). (**C**) Multicystic structures are present within the lesion (HE×200). (**D**) Micropapillary structures are identified in some cases (HE×400). (**E**) Papillary structures are observed in a minority of cases (HE×400). (**F**) Short spindle cell proliferation is seen in high-grade tumors (HE×400).

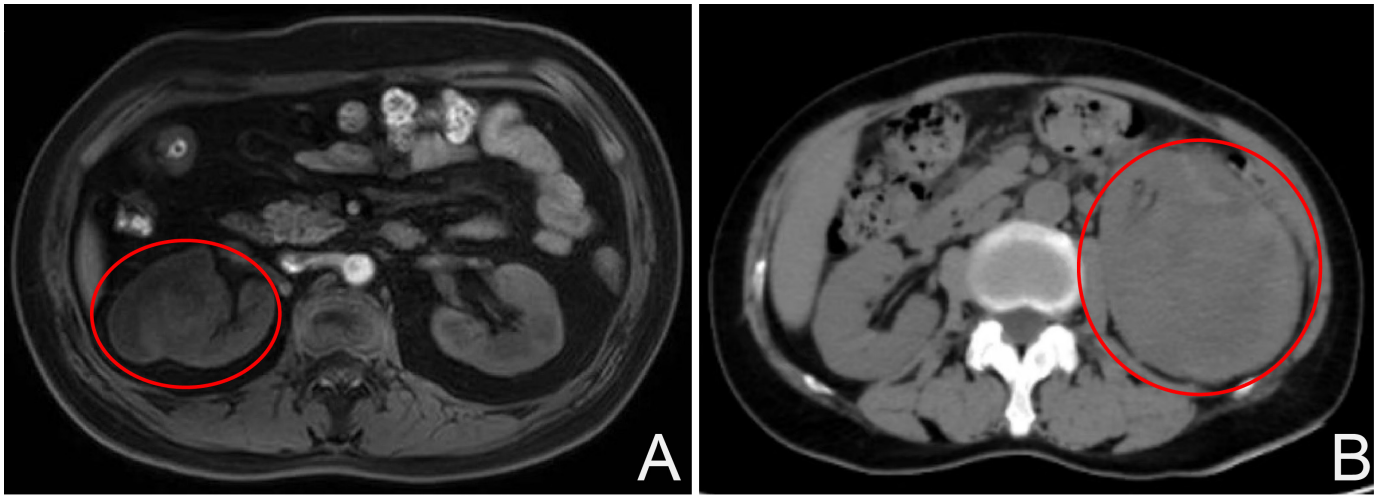

Figure 1. Imaging features of SDH-RCC. (A) CT shows a right renal mass; (**B**) CT shows a left renal mass.

With respect to cytomorphology, tumor cells exhibited abundant eosinophilic cytoplasm, with vacuolar changes noted focally in some cases. Focal short spindle-cell morphology was present in 1 case (case 14; Figure 2F). Nuclei were round to oval with fine, evenly distributed chromatin and mild nuclear atypia. A small number of cases showed more marked nuclear atypia, characterized by enlarged nuclei, coarse chromatin, occasional prominent nucleoli, and focal necrosis.

Of the 14 cases included in this study, 10 were classified as low-grade [International Society of Urological Pathology (ISUP)/WHO grade 1-2], and 4 as high-grade, including 3 cases of [ISUP/WHO grade 3] and 1 case of [ISUP/WHO grade 4].

Immunohistochemical Staining

Immunohistochemical staining was performed in all 14 cases (Table 2). The results showed that tumor cells in all cases were positive for PAX-8 (Figure 3A) and vimentin (Figure 3B). All cases were negative for SDHB (Figures 3C, D), while non-neoplastic renal tubules adjacent to the tumor were positive.

In addition, CK7, CA IX, and CD117 were all negative. The Ki-67 proliferation index ranged from 5% to 30%. All low-grade tumors exhibited a low Ki-67 index, ranging from 5% to 15% (Figure 3E), whereas the Ki-67 index of high-grade tumors was 20–30% (Figure 3F).

Follow-Up Results

Follow-up was conducted in all 14 patients, with a follow-up duration of 2-7 years. One patient was lost to follow-up, 1 patient was dead, and the remaining 12 patients were alive at the last follow-up. In addition, extrarenal metastasis occurred in 3 patients (cases 8, 13 and 14). Case 8 was found to have lung metastases during examination upon seeking medical attention for fever and cough 11 months after surgery, and case 13 was diagnosed with lung metastases during routine physical

Table 1. Clinicopathological information of 14 patients.

Number	Age	Sex	Location (kidney)	Size	Reason for consultation	Surgical approach	Cut surface of the mass	Metastasis status	Follow-up
1	50	Male	Right	2.5cm×2.0cm×2.0cm	Physical examination	Partial nephrectomy	Yellowish-gray, multiloculated cystic	None	Alive
2	53	Female	Right	5.0cm×4.0cm×1.5cm	Lumbar disc herniation	Radical nephrectomy	Grayish-white and grayish-red, slightly firm in texture	None	Lost to follow-up
3	78	Female	Right	7.5cm×5.0cm×4.5cm	Physical examination	Radical nephrectomy	Variegated appearance	None	Alive
4	48	Female	Right	6.5cm×5.0cm×3.5cm	Physical examination	Partial nephrectomy	Multiloculated cystic	None	Alive
5	48	Male	Left	6.0cm×5.0cm×4.0cm	Physical examination	Partial nephrectomy	Yellowish-gray and grayish-brown, firm in texture	None	Alive
6	43	Male	Right	3.2cm×3.2cm×2.8cm	Physical examination	Partial nephrectomy	Grayish-white and yellowish-gray, firm in texture	None	Alive
7	65	Male	Left	2.5cm×2.0cm×2.0cm	Physical e xamination	Partial nephrectomy	Yellowish-gray and grayish-brown	None	Alive
8	59	Female	Left	7.5cm×7.0cm×6.0cm	Left lower abdominal pain	Radical nephrectomy	Yellowish-gray and grayish-white, with a thin capsule	Pulmonary metastasis	Alive
9	49	Male	Left	3.5cm×3.0cm×1.5cm	Rapid weight loss, gastric discomfort	Partial nephrectomy	Grayish-white and grayish-brown, cystic and solid	None	Alive
10	56	Male	Left	5.0cm×5.0cm×4.0cm	Physical examination	Partial nephrectomy	Variegated, relatively well-circumscribed	None	Alive
11	50	Male	Left	4.5cm×3.2cm×2.7cm	Physical examination	Partial nephrectomy	Yellowish-gray and grayish-red, hemorrhagic cystic degeneration	None	Alive
12	58	Male	Left	1.5cm×1.5cm×1.2cm	Abnormal liver function	Partial nephrectomy	Yellowish-gray, with a capsule	None	Alive
13	53	Male	Right	8.0cm×7.0cm×7.0cm	Right inguinal hernia	Radical nephrectomy	Grayish-brown, medium in texture	Pulmonary metastasis	Alive
14	51	Male	Left	4.0cm×3.5cm×3.5cm	Low back pain with fever	Partial nephrectomy	Grayish-white, firm in texture	Lumbar spine metastasis	Death

examination 5 years after surgery. Case 14 developed bone metastasis and has died.

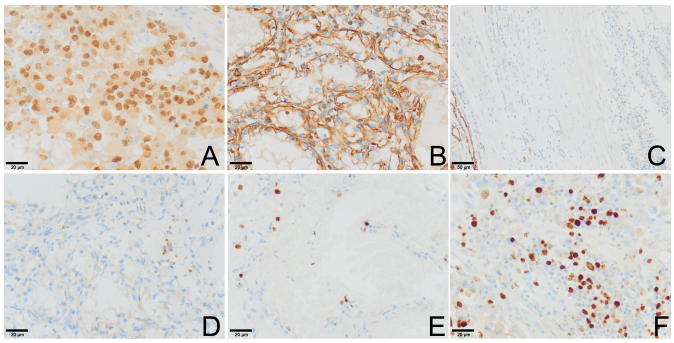

Figure 3. Immunohistochemical features of SDH-RCC. (A) Tumor cells show nuclear positivity for PAX-8 (EnVision×400). (**B**) Tumor cells are positive for Vimentin (EnVision×400). (**C**) SDHB staining: positive normal renal tubules (lower left), negative tumor cells (upper right) (EnVision×200). (**D**) SDHB staining is negative in tumor tissue (EnVision×400). (**E**) Low nuclear grade with low Ki-67 proliferation index (EnVision×400). (**F**) High nuclear grade with high Ki-67 proliferation index (EnVision×400).

Table 2. Results of immunohistochemical staining.

Number	Immunohistochemical staining items						
	SDHB	PAX-8	Vimentin	CK7	CD117	CAIX	Ki – 67
1	-	+	+	-	-	-	8%
2	-	+	+	-	-	-	10%
3	-	+	+	-	-	-	20%
4	-	+	+	-	-	-	10%
5	-	+	+	-	-	-	15%
6	-	+	+	-	-	-	8%
7	-	+	+	-	-	-	8%
8	-	+	+	-	-	-	25%
9	-	+	+	-	-	-	5%
10	-	+	+	-	-	-	10%
11	-	+	+	-	-	-	8%
12	-	+	+	-	-	-	7%
13	-	+	+	-	-	-	20%
14	-	+	+	-	-	-	25%

Note: - : negative; + : positive.

Discussion

SDH is a key enzyme in the tricarboxylic acid cycle that catalyzes the conversion of succinate to fumarate, and it is composed of four distinct subunits, including SDHA, SDHB, SDHC, and SDHD [1]. Mutations in any of the SDH subunits can lead to loss of normal function of the complex, thereby contributing to the development of associated tumors.

In 2004, Vanharanta et al. first identified familial genetic characteristics of SDHB gene mutations in 3 relatively young patients with RCC, and suggested a potential correlation between these mutations and the development of early-onset RCC. Subsequently, due to the limited number of cases, this type of RCC was not classified separately. It was not until 2016 that the WHO officially classified SDH-RCC as an independent subtype of RCC [5].

SDH-RCC is an extremely rare subtype of RCC, accounting for only 0.05%-0.2% of all RCC. It has a wide age distribution, ranging from 14 to 76 years, and shows a male predominance [3]. In this study, a total of 14 SDH-RCC patients were collected, with an age range of 43-78 years, including 10 males and 4 females. These findings were generally consistent with the age and gender distribution characteristics of SDH-RCC reported in the literature. Patients with SDH-RCC harbor mutations in the SDHA, SDHB, SDHC and SDHD genes, among which SDHB mutations are the most common [6-8]. In addition, germline mutations in SDH genes can cause patients to develop gastrointestinal stromal tumors, pheochromocytoma/paraganglioma, and pituitary adenomas [1]. No clinical records of these associated neoplasms were identified in the 14 patients included in this study.

Histologically, the tumors are mostly well-circumscribed, with variable cut surface colors ranging from gray-yellow to gray-red [9]. Microscopically, tumor cells are predominantly arranged in solid and nested patterns, often accompanied by the formation of microcystic, multicystic and tubular structures. Papillary structures may occasionally be observed. Tumor cells show abundant eosinophilic cytoplasm with vacuolar changes, and the nuclei are usually bland [9]. In the present series of 14 cases, typical solid sheet-like and nested structures were identified in all cases, and papillary structures were found in case 14. The cytomorphology was generally consistent with that described in the literature, except that focal short spindle-cell morphology was displayed in case 14. 10 cases were low-grade nuclear grade, and 4 cases were high-grade nuclear grade. In addition, SDH-RCC shows overlapping histomorphological features with other types of RCC, including clear cell RCC, papillary RCC and chromophobe RCC [1]. Sarcomatoid transformation may occur in high-grade SDH-RCC.

Regarding treatment and prognosis, most SDH-RCC are low-grade tumors with weak invasiveness and rare metastasis. The long-term metastasis rate is approximately 11%, and the overall prognosis is generally favorable. Treatment is generally performed with partial nephrectomy [6, 9]. In contrast, high-grade SDH-RCC, including tumors with sarcomatoid change, necrosis, and high nuclear grade, is relatively rare but the invasiveness of the tumor is significantly increased, and the tumor is prone to metastasis with a metastatic rate of up to 70%, resulting in a relatively poor prognosis. Radical nephrectomy is usually performed for these high-risk tumors [10]. In the present study, among the 14 patients, 1 patient was lost to follow-up. Of the remaining 13 patients, 12 were alive and 1 had died at the last follow-up. Notably, all 3 patients who developed extrarenal metastasis presented high nuclear-grade.

Differential diagnosis: 1. Clear cell RCC is the most common subtype, accounting for the highest incidence among all RCC. Tumor cells are arranged in solid nests or acinar structures, with a characteristic network of thin-walled blood vessels in the stroma [11]. The cells are large and polygonal, with abundant clear cytoplasm or eosinophilic cytoplasm in high-grade tumors [11]. Immunohistochemically, tumor cells are positive for CA IX, without loss of SDHB expression [9]. 2. Chromophobe RCC is the third most common subtype of RCC. Microscopically, tumor cells are mostly arranged in solid sheets and nests, with occasional tubular or trabecular patterns [12-13]. The tumor is composed of two cell types. One is small eosinophilic cells with granular cytoplasm and the other is large

polygonal cells with flocculent cytoplasm and characteristic plant-like cell membranes, showing wrinkled nuclei with inconspicuous nucleoli [13]. Immunohistochemically, tumor cells are positive for CK7 and CD117, without loss of SDHB [13]. 3. Oncocytoma is a benign renal tumor. Microscopically, tumor cells are densely arranged in nests, islands, and acini. The tumor stroma is often loosely edematous, accompanied by myxoid or collagenized changes, and a characteristic central scar composed of collagen fibers and compressed blood vessels may be present [14-15]. Tumor cells are round or cuboidal with indistinct cell borders, moderate to abundant cytoplasm containing dense eosinophilic granules, small nuclei, and inconspicuous nucleoli [14-15]. Immunohistochemically, tumor cells are positive for CD117 and negative for CK7, without loss of SDHB expression [9].

Conclusion

In summary, SDH-RCC is a rare subtype of RCC primarily caused by abnormal expression of the SDHB gene, which further leads to dysfunction of SDH. Among affected patients, those with low-grade SDH-RCC have a relatively more favorable prognosis but still require long-term follow-up and monitoring, whereas those with high-grade SDH-RCC are at a high risk of recurrence and metastasis. Currently, surgical resection remains the first-line treatment for SDH-RCC. Given the complex morphological features of SDH-RCC tumors, SDHB immunohistochemistry can assist in the diagnosis of this disease. In addition, it is recommended that family members of affected patients may undergo concurrent clinical counseling and screening to identify potential hereditary risks.

Abbreviations

SDH: Succinate dehydrogenase; SDH-RCC: Succinate dehydrogenase-deficient renal cell carcinoma; WHO: World Health Organization; ISUP: International Society of Urological Pathology.

Author Contribution

H.Q.Z.: Conception and design of the study, data analysis, and writing and critical review of the manuscript. **S.Z.H.** and **R.L.Z.**: Data collection and analysis, and draft of the manuscript. **S.J.L.** and **J.M.**: Data collection and analysis, and editing of the manuscript. All authors have approved the final manuscript.

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Ethics Approval and Consent to Participate

Not Applicable.

Competing Interests

The authors declare that they have no existing or potential commercial or financial relationships that could create a conflict of interest at the time of conducting this study.

Data Availability

The data used in this study are available from the corresponding author upon reasonable request.

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