

Metanephric adenoma in children: A case report and literature review

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Abstract. Metanephric adenoma (MA) is a rare type of benign renal epithelial tumor that can develop at any age. Nonetheless, MA is extremely rare in children and only a few cases have been reported to date. The present study aimed to report the case of a 5-year-old female found to have a mass in the right kidney during a routine pre-enrollment physical examination. Computed tomography (CT) images revealed multiple high-density calcifications in the mass, and contrast-enhanced CT and magnetic resonance imaging demonstrated that the mass was significantly enhanced in the cortical phase and decreased in the medullary phase. Based on these findings, the mass was initially diagnosed as angiomyolipoma before surgery; however, postoperative pathology confirmed the mass to be a MA. MAs are typically a type of soft tissue mass with relatively uniform density or signal, showing delayed enhancement in contrast-enhanced scanning. However, the mass found in the present study presented diffused high-density calcification, which was obvious in the early phase of contrast-enhanced scanning but weakened in the delayed enhancement phase. In conclusion, the present case study demonstrated that MA should be considered as one of the imaging differential diagnoses of fat-poor angiomyolipoma, renal carcinoma and oncocytoma.

Introduction

Primary renal epithelial tumors are typically malignant, whereas benign adenomas are rare. Metanephric adenomas (MAs) are a rare type of tumor, accounting for 0.2% of adult

renal epithelial tumors. Although MA can occur at any age, it is more common in women aged 50–60 years. MA is extremely rare in children, with only a few cases reported to date. Most patients with MA display no obvious clinical symptoms and they often seek medical treatment due to physical examination or incidental findings. Only a small number of patients report lower back pain, presence of an abdominal mass or gross or microscopic hematuria (1). The present study aimed to report a case of a 5-year-old female patient found to have a space-occupying mass in the right kidney during a routine pre-enrollment physical examination. Computed tomography (CT) scan images revealed multiple high-density calcifications in the mass and contrast-enhanced CT and magnetic resonance imaging (MRI) demonstrated that the mass was significantly enhanced in the cortical phase and decreased in the medullary phase. Based on these findings, the mass was first diagnosed as an angiomyolipoma before surgery, while postoperative pathology confirmed it to be a MA.

Case report

A 5-year-old female presented to The Affiliated Hospital of Zunyi Medical University for a routine physical examination. The physical examination revealed a hard palpable mass on the right side of the abdomen, without tenderness, rebound pain or muscle tension. The patient had no previous clinical signs such as waist pain, frequent urination, urgency, dysuria or gross hematuria. A kidney B-ultrasound demonstrated a mass in the patient's right kidney in August 2019. Laboratory testing revealed an elevated level of carbohydrate antigen 19-9 level at a value of 128.4 (expected value <25). Additional tumor markers and routine blood examination values were within the expected reference value range. CT scan showed that the mass was clearly demarcated from the surrounding normal renal parenchyma and multiple high-density calcifications were observed inside. Contrast-enhanced CT scan and MRI showed that the tumor in the cortical stage was greatly enhanced, while in the medullary stage, it was significantly weakened (Fig. 1). These imaging findings were different from those of the majority of renal malignant tumors, including nephroblastoma, neuroblastoma, and renal carcinoma, with cystic necrosis often visible in the tumors, and therefore a fat-poor renal angiomyolipoma (RAML) was considered. A

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preoperative needle biopsy was not performed as the family of the patient opted for an intraoperative frozen biopsy and the patient subsequently underwent a tumor resection under general anesthesia at 13 days post-admission.

During the operation, a piece of tumor tissue was removed, washed and dried with distilled water, and the tumor tissue sections were placed on the frozen section machine table. The temperature was adjusted to -20°C and the tissues were frozen for ~ 3 min. The diseased tissue was cut into 3- to 5- μm slices, and the frozen slices were treated using a hematoxylin-eosin staining method. After staining, the slices were placed under an optical microscope for observation at x400 magnification. Under the microscope, the size of the tumor cells was relatively consistent and they were mainly arranged in an acinar-like pattern (Fig. 2). The tumor cells were small in size, with little cytoplasm, round or oval nuclei and no nucleoli and mitoses. Based on these pathological findings, the patient was considered to have a benign tumor. After the surgery, the excised tumor tissue was sent to the pathology department for further immunohistochemistry (all specimens were fixed with 10% neutral formalin, dehydrated at room temperature for ~ 24 h and paraffin embedded. The 3- to 4- μm thick sections were stained for creatine kinase, vimentin, paired box protein 8, Wilm's tumor 1, cluster of differentiation 10, epithelial membrane antigen and CD56, with antibodies purchased from MXB Biotechnologies, and viewed at x400 magnification under an optical microscope) and the results showed that tumor cells positively expressed CK, vimentin, PAX-8, WT-1 and CD10, but did not express EMA and CD56, and the Ki-67 index was $<1\%$. Based on these results, the patient was diagnosed with MA. The patient underwent no further treatment following surgical resection of the tumor due to the benign nature of MAs. The patient attended follow-up appointments for 2 years and the patient's parents reported that the patient had no discomfort.

Literature review

The PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Embase (<https://www.embase.com/>) and Web of Science databases (<https://www.webofscience.com/wos/woscc/basic-search>) (as of September 1, 2022), were searched for case reports and case series of pediatric patients with MA. Language restrictions were limited to English. For each relevant case report, the first author, publication year and country, as well as the patient's age, sex, main clinical symptoms, tumor location (left or right), CT and MRI imaging findings, immunohistochemical results, treatment methods and follow-up results were recorded (Table I).

SPSS software (version 18.0; IBM Corp.) was used for data analysis. The measurement data conforming to the normal distribution were presented as the mean \pm standard deviation. The non-normal distribution was presented as the median (upper and lower quartiles). The chi-squared test was used to compare the data between groups. $P < 0.05$ was considered to indicate a statistically significant difference.

A systematic database search showed that 27 studies reported MA in pediatric patients prior to the case reported in the present study (2-28), resulting in a total of 28 pediatric patients with MA. Of these, 13 patients were male and 15 were female. The proportion of Caucasian patients ($n=20$) was

significantly higher compared with Xanthoderm patients ($n=8$). No significant difference was demonstrated between patients with a left or right tumor location. One patient had MAs in both kidneys (26). In most patients, MA was found after a routine physical examination, abdominal pain or diarrhea. Rare clinical symptoms and signs included hematuria, urinary tract infection, polycythemia, chyluria and proteinuria. The maximum diameter of tumors ranged from 1.0-15.5 cm, but most tumors were <5.0 cm in diameter at the time of diagnosis. In the available data, the density and signal of most tumors on CT or MRI was heterogeneous (13/19) and the probability of cystic change was slightly higher than that of calcification (Table II). Only a few studies reported MRI findings related to MA, which usually showed a low signal on T1-weighted imaging (T1WI) and hypo-to-hypersignal on T2-weighted imaging (T2WI). Most tumors displayed hypo-enhancement on contrast-enhanced CT or T1WI and some patients showed progressive enhancement during delayed scanning.

The immunohistochemistry staining results of the tissues of 17 patients with MA in 17 cases were analyzed. These results demonstrated that almost all tumors positively expressed WT-1 and most of the tumors positively expressed vimentin, CD56 and CD57 and almost negatively expressed EMA, S100, and so forth. The majority of the 28 patients with MA underwent partial nephrectomy. In some cases, the tumors were considered as nephroblastoma or could not be identified before surgery. These patients underwent radical nephrectomy. None of these patients showed signs of recurrence during follow-up because of the benign nature of MA.

Discussion

MA was first reported by Bove *et al* in 1979 (29) and named by Brisigotti *et al* (30) in 1992. MA tends to occur in the renal cortex and its histological origin remains unclear. The World Health Organization's histopathological classification of renal tumors classified MA, metanephric adenofibroma and metanephric stromal tumors as metanephric tumors and their biological symptoms as benign (31). The disease can occur at any age but is more common in women aged 50-60 years (32). The incidence of MA in children is extremely rare (9,31), with only 27 cases reported in the literature before the present study. Most of the patients with MA have no obvious clinical symptoms and they often seek medical treatment after a physical examination or incidental findings. Only a few patients may have low back pain, abdominal mass or gross or microscopic hematuria (1). The patient in the present study was a 5-year-old female whose kidney mass was discovered incidentally during a routine pre-enrollment physical examination.

Imaging examinations, including B-ultrasound, CT and MRI, serve a significant role in the diagnosis and differential diagnosis of renal tumors. The ultrasonographic appearance of MAs may be a well-circumscribed hyperechoic, anechoic or hypoechoic solid mass, with few intratumoral blood vessels (33). CT images indicate that most of these tumors are soft tissue masses with a clear boundary and uniform density, the mass has cystic or/and calcification and the density is not uniform. Larger masses protrude from the kidney outline and grow outward. On contrast-enhanced scans, the tumors mostly demonstrate mild enhancement in the cortical phase

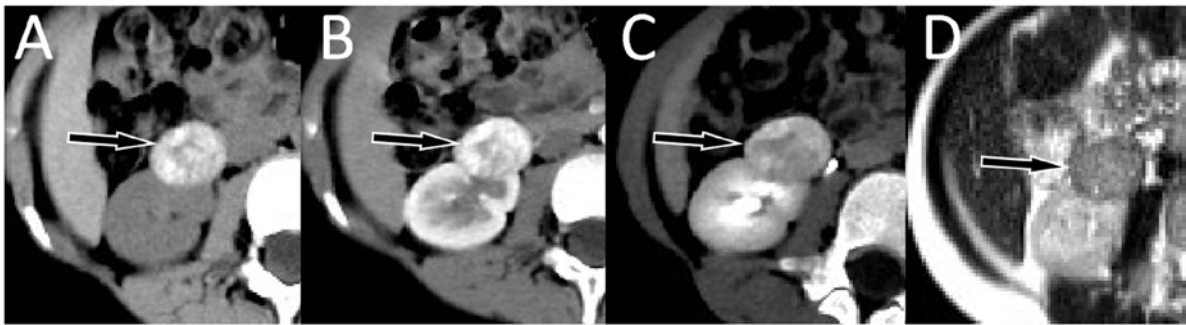


Figure 1. Scan images of the patient's mass. (A) Computed tomography plain scan showed an uneven high-density mass about 2.0x2.4x3.0 cm in size in the lower pole of the right kidney, protruding outside the outline of the kidney. (B) Contrast-enhanced cortical phase showed marked enhancement of the lesion, similar to that of the adjacent renal cortex. (C) Decreased degree of enhancement in the medullary phase. (D) T2-weighted imaging sequence of magnetic resonance imaging showed that the signal of the lesion was slightly lower than that of the adjacent renal parenchyma.

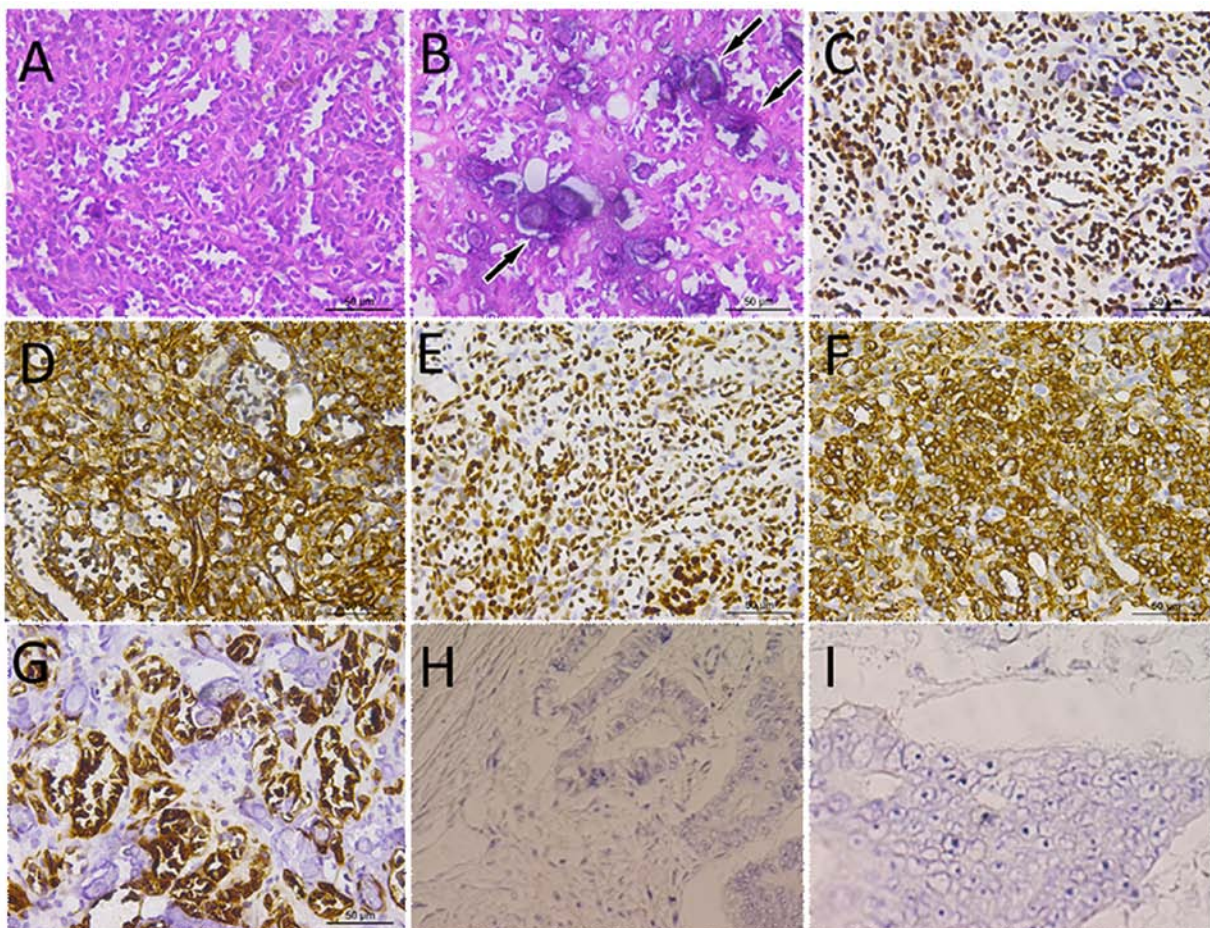


Figure 2. Staining of patient tumor tissue. (A) H&E staining showed that the size of the tumor cells was relatively consistent, mainly in acinar-like arrangement, and the tumor cells were small in size, with little cytoplasm, round or oval nuclei, and no nucleoli and mitoses. (B) H&E staining showed blue-stained calcifications (arrows) observed under high magnification. Immunohistochemical staining of tumor tissues showing cells expressing (C) Wilms tumor 1, (D) vimentin, (E) PAX-8, (F) WT-1 and (G) CD10, but negatively expressing (H) EMA and (I) CD56. H&E, hematoxylin and eosin.

and progressive enhancement in the medullary and delayed phases and the enhancement degree is lower than that of the surrounding normal renal parenchyma. Tumors appear hypointense on T1WI and hypointense to hyperintense on T2WI compared with the adjacent renal parenchyma on MRI. The tumors are predominantly hyperintense compared with adjacent renal parenchyma on fat-suppressed T2WI and diffusion-weighted imaging (DWI) (10,33).

The patient in the present study presented with a high-density mass protruding out of the kidney contour on CT and decreased enhancement of delayed phase on contrast-enhanced scan, which was similar to the imaging findings of fat-poor RAML. The T1WI, T2WI and DWI sequences of MRI showed heterogeneous low-signal changes, which were different from the imaging findings of typical MA as the mass of the patient in the present study had diffuse calcification.

Table I. Clinical and imaging features of the cases of children with MA based on the literature review and the present study.

First author, year	Country	Patient sex, age, (years)	Main symptoms	Tumor location	CT/MRI				Maximum diameter, cm	Immunohistochemistry results	Treatment	Follow-up results (Refs.)			
					Density/signal	Calcification	Cystic	T1WI					T2WI	DWI	CECT/MRI
Benson <i>et al</i> , 2018	USA	F, 10	Abdominal pain for 1 week	R	Heterogeneous	+	+	Hypo	Hyper	Hypo-enhancement	3.3	WT-1 (+), CD57 (+), CD56 (+), TTF1 (+), CK7 (-), EMA (-), S100 (-)	PN	NA	(2)
Küpelci <i>et al</i> , 2009	Turkey	F, 6	Abdominal pain, polyuria	R	Heterogeneous	+	+	NA	NA	NA	6.5	WT-1 (+), NSE (+), CD57 (+), CD56 (+), K7 (-)	PN	24 months without recurrence	(3)
Sarhan <i>et al</i> , 2022	Egypt	M, 1.75	Abdominal distension, polyuria	L	Homogenous	-	-	NA	NA	Hypo-enhancement	2.0	WT-1 (+), CD57 (+)	PN	12 months without recurrence	(4)
Amodio <i>et al</i> , 2005	USA	F, 8	Nausea, vomiting, diarrhea for 2 days	L	Heterogeneous	+	+	Hypo	NA	NA	3.0	NA	TN	NA	(5)
Bastos <i>et al</i> , 2007	Brazil	F, 2	Urinary tract infection	L	Heterogeneous	+	-	NA	NA	NA	4.0	NA	TN	15 months without recurrence	(6)
Drut <i>et al</i> , 2001	Argentina	F, 11	Hematuria	L	NA	NA	NA	NA	NA	NA	4.5	NA	TN	NA	(8)
Hu <i>et al</i> , 2022	P.R. China	M, 2	Occasionally found	L	Homogenous	-	-	Iso	Slightly hyper	Delayed reinforcement	5.4	Vim (+), CK (+), WT-1 (+), CD99 (+), INI-1 (+), PAX-8 (+), CD56 (+), CD57 (+), CD10 (-), S100 (-)	PN + Ch	NA	(9)
Jiang <i>et al</i> , 2019	P.R. China	M, 3	Back pain	R	Heterogeneous	-	+	Hypo	Hyper	Delayed reinforcement	4.5	NA	PN	48 months without recurrence	(10)
Kohashi <i>et al</i> , 2009	Japan	M, 9	Hematuria	L	NA	NA	NA	NA	NA	NA	1.9	Vim (+), CK (+), WT-1 (+), CK7 (-), EMA (-)	TN	12 months without recurrence	(11)

Table I. Continued.

First author, year	Country	Patient sex, age, years	Main symptoms	Tumor location	CT/MRI				Maximum diameter, cm	Immunohisto-chemistry results	Treatment	Follow-up results (Refs.)
					Density/signal	Calcification	Cystic	DWI				
Loeser <i>et al</i> , 2009	Germany	F, 2	Hematuria	L	Heterogeneous	NA	NA	NA	Hypo-enhancement	PN	No recurrence	(12)
Portugal and Barroca, 2008	Portugal	F, 8	Abdominal mass	R	NA	NA	NA	NA	NA	TN	NA	(13)
McNeil <i>et al</i> , 2008	USA	M, 5	Chyluria	L	NA	NA	NA	NA	NA	TN	12 months without recurrence	(14)
Rakheja <i>et al</i> , 2005	USA	M, 10	Hematuria	R	NA	NA	NA	NA	NA	PN	NA	(15)
Ünal <i>et al</i> , 2020	Turkey	M, 7.5	Anorexia	NA	NA	NA	NA	NA	NA	TN	No recurrence	(16)
Zhang <i>et al</i> , 2020	P.R. China	M, 11	Occasionally found	R	NA	NA	NA	NA	NA	PN	92 months without recurrence	(17)
Keshani de Silva <i>et al</i> , 2000	USA	M, 9	Proteinuria	L	NA	NA	NA	NA	NA	TN	NA	(18)
Renshaw <i>et al</i> , 2000	USA	F, 7	Hematuria	L	Heterogeneous	-	+	NA	NA	TN + Ch	2 months without recurrence	(19)
Navarro <i>et al</i> , 1999	Canada	F, 9	Urinary tract infection	R	Heterogeneous	-	+	NA	Hyper-enhancement	PN	No recurrence	(20)
Mahoney <i>et al</i> , 1997	USA	F, 2	Lethargy, polydipsia	R	Homogenous	-	-	NA	Did not enhance	PN	No recurrence	(21)
Le Nué <i>et al</i> , 2011	France	F, 4	Increased red blood cells	R	Heterogeneous	+	-	Iso	Hypo-enhancement	PN	24 months without recurrence	(22)

Table I. Continued.

First author, year	Country	Patient sex, age, (years)	Main symptoms	Tumor location	CT/MRI				Maximum diameter, cm	Immunohistochemistry results	Treatment	Follow-up results (Refs.)
					Density/signal	Calcification	Cystic	DWI				
Barroca <i>et al</i> , 2016	Portugal	M, 8	Vomiting, abdominal pain	R	Homogenous	-	-	NA	NA	TN	NA (23)	
Mei <i>et al</i> , 2010	P.R. China	F, 2	Occasionally found	R	Heterogeneous	+	+	Hypo	Hypo-enhancement	PN	14 months without recurrence (24)	
Davis <i>et al</i> , 1995	USA	F, 10	NA	R	NA	NA	NA	NA	NA	PN	No recurrence (7)	
Ozden <i>et al</i> , 2015	Turkey	M, 10	Occasionally found	R	Homogenous	-	-	Hypo	Hypo-enhancement	PN	18 months without recurrence (25)	
Pasricha <i>et al</i> , 2012	India	M, 4	Abdominal pain and distension for 2 months	Bilateral	Homogenous	-	+	NA	Hypo-enhancement	TN	8 months without recurrence (26)	
Spaner <i>et al</i> , 2014	Canada	M, 7	Occasionally found	L	Heterogeneous	+	+	NA	Delayed reinforcement	PN	NA (27)	
Yin <i>et al</i> , 2015	P.R. China	F, 0.2	Prenatal check-up	L	Heterogeneous	-	+	Hypo	Hypo-enhancement	TN	18 months without recurrence (28)	
Present study	P.R. China	F, 5	Occasionally found	R	Heterogeneous	+	+	Hypo	Fast in fast out	PN	24 months without recurrence	

hypo-, iso- and hyper- refer to hypodensity, isodensity, hyperdensity for CT or hyposignal, isosignal, hypersignal for MRI, respectively. M, male; F, female; R, right; L, left; PN, partial nephrectomy; TN, total nephrectomy; CT, computed tomography; MRI, magnetic resonance imaging; CECT, contrast enhancement computed tomography; Ch, chemotherapy; -, negative; +, positive; NA, not applicable.

Table II. Distribution and imaging findings of metanephric adenoma in children.

Parameters	Proportion of patients, n/total n (%)	P-value
Patient sex		0.496
Male	13/28 (46.4)	
Female	15/28 (53.6)	
Patient ethnicity		<0.001
Xanthoderm	8/28 (28.6)	
Caucasian	20/28 (71.4)	
Tumor density		0.027
Heterogeneity	13/19 (68.4)	
Homogeneity	6/19 (31.6)	
Calcification		0.816
Yes	8/18 (44.4)	
No	10/18 (55.6)	
Cystic change		0.342
Yes	11/18 (61.1)	
No	7/18 (38.9)	
Maximum diameter, cm		<0.001
<5.0	20/28 (71.4)	
≥5.0	8/28 (28.6)	

As the patient in the present study had a mass with diffuse calcification, it was necessary to differentiate the mass from fat-poor RAML. RAML comprises varying proportions of fat, smooth muscle and abnormal blood vessels. It is sometimes difficult to diagnose on imaging because of the lack of fat or less fat. Fat-poor RAMLs have a slightly high density on CT and enhanced scan usually shows uniform enhancement, the degree of enhancement in the delayed phase is reduced and T2WI shows uniform, slightly low signals or a few patchy high signals (34,35). In addition, MA should also be differentiated from renal carcinoma, Wilms tumor (WT), renal oncocytoma (RO) and neuroblastoma.

Renal carcinoma is the most common type of clear cell carcinoma. It is more common in adults and mostly occurs in the renal cortex. CT plain scan images demonstrate that these tumors are mostly isodense and low-density cystic degeneration, necrosis and high-density calcification are often seen in the tumor. Contrast-enhanced scans demonstrate obvious uneven enhancement in the early stage. This enhancement gradually decreases in the middle and late stages, which is a typical 'fast-in, fast-out' performance (36). Chromophobe carcinoma and clear cell carcinoma demonstrate similar imaging manifestations, but central spoke scars can also be seen in MRI images with larger tumor volumes being associated with increased numbers of spoke scars (36). Renal papillary carcinoma has a lower degree of enhancement on contrast-enhanced scans than the renal parenchyma, but the enhancement lasts longer and is progressive (36-38). WT is the most common renal malignant tumor in children. According to statistics, in the 10 years from 2005 to 2014, the incidence of nephroblastoma in developing countries was ~1 in 8,000 (39).

On CT or MRI images, WT mostly appears as a large mass with equal or slightly low density and signal (40). Necrosis, cystic degeneration and hemorrhage are common in the tumor and calcification can be seen in some lesions (40). RO is another type of rare benign tumor of the kidney, accounting for only 7% of kidney tumors in the United States between 1980 and 1995, which tends to occur in middle-aged and elderly men and mostly originates from the renal cortex (41). On CT images, RO appears as a well-,circumscribed soft tissue mass which protrudes beyond the renal contour. Contrast-enhanced scans show lower enhancement than normal renal parenchyma in both early and late phases (42). Some lesions show central stellate scar sign and segmental enhancement inversion sign, which are relatively specific to RO (43). Neuroblastoma is a malignant tumor that occurs more frequently in children and is less common in the kidneys, the incidence rate in the United States was 10.5/10⁶ between 1990 and 2002 (44). A typical renal neuroblastoma is a large, lobulated soft tissue mass that is prone to necrosis, cystic degeneration and hemorrhage. It is likely to be accompanied by calcification, which is usually characterized by sandy or large-area calcification (45). The mass is likely to surround and bury the renal blood vessels (46).

The diagnosis of MA is mainly based on histopathological examination. Microscopically, small and uniform tumor cells are seen in an acinar-like arrangement, with little cytoplasm, fine chromatin, no or inconspicuous nucleoli and rare mitoses (47). Most previously reported MA cases were positive for WT-1, CD57, CD56, AE1/AE3, CAM5.2, CK18 and vimentin, negative for EMA, NSE, CEA, CgA, Syn and P504S and focally positive or negative for CK7 (11,48). The microscopic structural features of the patient in the present study were consistent with the aforementioned literature. The immunohistochemical staining results demonstrated that the tumor cells positively expressed CK, vimentin, PAX-8, WT-1 and CD10, but did not express EMA and CD56. Therefore, these results were consistent with the diagnosis of MA.

Surgical resection of the tumor is the main treatment method for MA and the surgical method has gradually changed from nephrectomy to nephron-sparing surgery due to the benign nature of the tumor (25,49). For patients who experience difficulties obtaining a clinical diagnosis, percutaneous biopsy cytology examination has certain clinical significance, and radical nephrectomy cannot be blindly performed. Intraoperative frozen pathological examination can clarify the diagnosis and aid in selection of an appropriate surgical method, which is an ideal diagnostic tools that can minimize the occurrence of missed diagnosis and mistreatment and avoid the need to perform a total nephrectomy (17). A previous study reported that MA can be treated with a chemotherapy regimen also used to treat WT (9). Overall, MA has a good prognosis and even with a small number of cases of malignant MA reported in previous studies, no recurrence has been reported during follow-up (8,19,50). The patient in the present study had no complaints of discomfort during the 2-year follow-up period following surgical removal of the mass. A limitation of current study is that the quality of the MR images was relatively low, so only T2WI sequences are presented in the article.

In conclusion, MA is a rare benign kidney tumor with a low incidence in children. The typical imaging appearance of

MA is a soft tissue mass with relatively homogeneous density or signal and delayed enhancement on contrast-enhanced scans. However, the patient in the present study presented with heterogeneous hyperdensity, with marked enhancement in the early phase of contrast-enhanced scans and decreased enhancement in the delayed phase. Therefore, the present case study demonstrated that MA should be considered as one of the imaging differential diagnoses of fat-poor angiomyolipoma, renal carcinoma, oncocytoma and the like. Moreover, a preoperative correct understanding of MA can avoid unnecessary radical nephrectomy.

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Availability of data and materials

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

Authors' contributions

XH, WL, DL, JC and JB conceived and designed the study. PW, JC and XH acquired, analyzed and interpreted the data. PW and JC confirm the authenticity of all the raw data. XH and WL drafted the manuscript. JC and PW critically revised the manuscript for important intellectual content and gave final approval of the version to be published. All authors agreed to the journal to which the article was submitted and agreed to take responsibility for all aspects of the work. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Affiliated Hospital of Zunyi Medical University (approval no. KLL-2023-102).

Patient consent for publication

Written informed consent was obtained from both parents of the patient to publish this case report.

Competing interests

The authors declare that they have no competing interests.

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