

# Experience of diagnosis and management of metanephric adenoma: retrospectively analysis of 10 cases and a literature review

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**Background:** Metanephric adenoma (MA) is a rare benign tumor with only several hundred cases reported worldwide to date. Herein, we retrospectively summarized the experience of diagnosis and management of ten MA cases.

**Methods:** A total of ten MA patients were included in this study definitely diagnosed by postoperative immunohistochemistry at the First Affiliated Hospital of Nanjing Medical University from January 2010 to January 2019. Clinical characteristics, image features, therapeutic procedures, histological diagnosis and outcomes of them were retrospectively analyzed.

**Results:** Characteristics of the patient population were nine females and one male with age of 36.8±17.5 years. The mean tumor size was 33.6 mm (range from 35.0 to 70.0 mm). Among them, nine cases were asymptomatic and one case showed acute flank pain. All ten cases underwent plain and enhanced computed tomography (CT) scan. Laparoscopic partial nephrectomy (LPN) was performed in seven cases and laparoscopic radical nephrectomy (LRN) was applied in the other three cases. Postoperative routine pathology results confirmed that seven cases were MA. However, two patients were misdiagnosed with papillary renal cell carcinoma (PRCC), and another was misdiagnosed with Wilms' tumor. Further immunohistochemistry eventually confirmed all these ten cases as MA. During a mean follow-up of 58.3 month, all ten patients were alive with no local recurrences nor metastases.

**Conclusions:** In summary, MA is a rare benign tumor with no distinct clinical symptoms. The definite diagnosis depends on the postoperative pathological findings. Fortunately, due to its non-malignant nature, patients always have a good prognosis.

Keywords: Metanephric adenoma (MA); benign tumor; laparoscopic partial nephrectomy (LPN)

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# Introduction

Metanephric adenoma (MA), which derives from the embryonic tissue of the nephritic medulla, is a very rare benign tumor accounting for about 0.2-0.7% of adult renal epithelial neoplasms (1,2). To date, just a few hundred MA cases were reported in the literature and showed obvious female predominance (female: male =2:1). Clinical symptoms and signs of MA include abdominal mass, pain, hematuria, polycythemia and so on. However, most MA patients are asymptomatic and the lesions are always accidentally discovered in their health checkup by an ultrasound examination (3). Further abdominal computerized tomography (CT) or Magnetic Resonance Imaging (MRI) examination are essential for the diagnosis. Whereas, due to no specific imaging features or clinical manifestation compared with other renal malignancies, like Wilms tumor (WT) or papillary renal cell carcinoma (PRCC), the diagnosis of MA is always confirmed according to postoperative pathological results (4,5). What's more, it is difficult to distinguish MA from some nephritic malignancy by intraoperative pathological diagnosis, while further postoperative pathology or immunohistochemistry can confirm the disease (6). Therefore, it brings challenges to urologists to make a definite diagnosis of MA and choose better surgical procedures for MA patients.

Due to the lack of sufficient awareness and experience of MA, it may lead to potential misdiagnosis and inadequate treatment. More experience is in demand to share with peers. Herein, we retrospectively analyzed the clinical characteristics, image features, therapeutic procedures, histological diagnosis and outcomes of ten MA cases treated in our hospital from 2010 to 2019. Moreover, we performed a brief literature review to the diagnosis and management of MA to provide a comprehensive understanding of this uncommon tumor.

We present the following article in accordance with the STROBE reporting checklist (7) (available at http://dx.doi. org/10.21037/tau-19-912).

# Methods

# Patients

A total of ten MA patients who were definitely diagnosed by postoperative pathology at the First Affiliated Hospital of Nanjing Medical University from January 2010 to January 2019 were included in this study. We retrospectively summarized the experience of diagnosis and management

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of them. We summarized and compared the year and the gender, clinical symptoms, tumor sizes, results of imaging examination, results of pathological examination, surgical methods and outcomes of these patients.

All procedures performed in this study were in accordance with the Declaration of Helsinki (as revised in 2013) and this study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (No. 2019-SR-312) and written informed consent for publication of the patients' information and images was entirely obtained.

### Imaging and pathological examination

All the ten cases received ultrasonography, as well as plain and enhanced CT scan. Five cases of them were further assessed by computed tomography angiography (CTA) examination, and two cases accepted MRI imaging. Intraoperative rapid pathology, postoperative routine histopathology and immunohistochemistry were used among all cases. Renal needle biopsy was adopted in two cases preoperatively.

# Surgical treatment and follow-up

Laparoscopic partial nephrectomy (LPN) was performed in seven cases while laparoscopic radical nephrectomy (LRN) was selected for the other three cases. All patients acquired complete postoperative follow-up with regular evaluation of Ultrasonography and CT.

### Statistical analysis

All the data were analyzed by Microsoft Excel, with a mean value and standard deviation (SD).

### Results

### Characteristics of subjects

*Table 1* displayed the general characteristics of the ten cases. Nine females and one male were diagnosed with MA and treated in our hospital from January 2010 to January 2019. The average age of patients was 36.8 years (ranging from 11 to 67 years). Only in one case, the tumor was found in left kidney, while the other nine cases of tumors located in the right side. Additionally, almost all patients had no obvious clinical symptoms and admitted to hospital due to

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Number	Gender	Age (years)	Side	Symptoms	Size (cm)	Preoperative diagnosis	Treatment	Operative time (min)	Post-operative hospitalization (days)	Follow-up (months)	Metastasis/ recurrence	Pathological diagnosis
1	Female	22	Right	No	7	Renal occupied lesions	LRN	120	3	2	No	MA
2	Female	65	Right	No	2.3	Renal occupied lesions	LPN	90	6	12	No	MA
3	Female	23	Right	No	3.5	Renal occupied lesions	LPN	100	7	91	No	MA
4	Male	46	Right	No	2.7	Renal occupied lesions	LPN	90	9	78	No	PRCC
5	Female	25	Left	No	3.5	Renal occupied lesions	LPN	150	9	42	No	WT
6	Female	30	Right	Pain	3	MA?	LRN	175	5	3	No	MA
7	Female	39	Right	No	4	Renal occupied lesions	LPN	95	9	94	No	MA
8	Female	67	Right	No	2.5	MA?	LRN	175	7	93	No	MA/PRCC
9	Male	11	Right	No	3	Renal occupied lesions	LPN	65	8	92	No	MA
10	Female	40	Right	No	2.1	Renal occupied lesions	LPN	100	7	76	No	MA/PRCC

Table 1 Characteristics of the 10 MA patients

LPN, laparoscopic partial nephrectomy; LRN, laparoscopic radical nephrectomy; MA, metanephric adenoma; WT, Wilms tumor; PRCC, papillary renal cell carcinoma; MA/PRCC, metanephric adenoma or papillary renal cell carcinoma.

ultrasonography findings, except for one patient complained with acute flank pain and was found a 3 cm renal mass on a kidney with severe hydronephrosis, caused by a 2.5 cm renal stone by ultrasonography. What's more, no polycythemia was found in any case. All patients have no specific family history.

# Imaging examination

Plain and enhanced CT scan was the primary imaging examination of the ten MA patients. Eight of the tumors appeared as isodense (equal to the normal renal parenchyma) while two as hypodense (lower than the normal renal parenchyma) in CT plain. Dynamic contrastenhanced CT revealed that enhanced degree of the tumors were all lower than that of the normal renal parenchyma. The average size of the tumors was  $33.6\pm13.4$  mm (range from 25 to 70 mm). *Figure 1* exhibited the CT feature of the tumor from a 65-year-old woman. Plain CT showed a round homogeneous isopycnic mass while the enhanced CT showed a progressive enhanced low-density mass with a diameter of 2.3 cm. What's more, *Figure 2* displayed the CT finding of a 22-year-old girl with a tumor about 7 cm in diameter. The enhanced CT revealed a well-defined inhomogeneous mass with internal cystic degeneration and progressive enhancement both in cortex phase and parenchymal phase.



Figure 1 The CT finding of a 65-year-old woman. Plain CT showed a round homogeneous isopycnic mass (A) while the enhanced CT showed a progressive enhanced low-density mass (B) with a diameter of 2.3 cm.



**Figure 2** The CT finding of a 22-year-old girl with a tumor about 7 cm in in diameter. Plain CT (A), enhanced CT in cortex phase (B) and parenchymal phase (C), and three-dimensional reconstructing of enhanced CT (D).

# Surgical treatment

Minimally invasive laparoscopic operation was applied in all cases. LPN was performed in 7 cases and the other 3 cases underwent LRN. The average surgical time was  $116\pm 36$  min (range from 65 to 175 mm). The average hospitalized days after surgery were  $7\pm 1.8$  days (range from 3 to 9 days). No severe complications happened to patients. *Figure 3* displayed the tumor in kidney excised by LRN of a 22-year-old girl, in the center of which revealed liquefactive necrosis.

# Pathological characteristics

Postoperative routine pathology showed that all the tumors



Figure 3 A tumor in renal excised during LRN of a 22-year-old girl. (A) Lateral; (B) Longitudinal-section. LRN, laparoscopic radical nephrectomy.

had entire capsules, and 7 cases were diagnosis as MA. While 2 cases were misdiagnosed as PRCC, and one case was misdiagnosed as WT. Microscopically, the morphology of tumor cells was uniform, with little eosinophilic cytoplasm and non-prominent nucleoli. Moreover, tumor cells showed tubular and acinar architecture, leading to the formation of glomerular-like or bud-like structures. Representative histopathology findings of the resect specimen of MA were shown in *Figure 4*.

Further immunohistochemistry confirmed all cases. Most tumor cells were positive for WT-1(WT1 transcription factor), CD57 (beta-1,3-glucuronyltransferase 1), Vimentin, Ckpan, Pax-8 (paired box 8) and E-Cadherin while negative for NSE (neuron-specific enolase), CK7 (keratin 7), CD10 (membrane metalloendopeptidase), EMA (endosomal maturation defective) and AMACR (alphamethylacyl-CoA racemase). Positive WT-1 and CD57, as well as negative CK7 and AMACR are characterized marks of MA. However, two cases exhibited a discordant immunophenotyped: one was negative for WT-1, another was positive for CK7.

# Follow-up and prognosis

During a mean follow up of 58.3 month (3-94 months),

all ten patients were alive with no local recurrences nor metastases confirmed by CT.

# **Discussion**

The first case of MA was described as a bilateral and diffuse tumor by Bove et al. in 1979, who identified MA as a variant of nephroblastoma (8). In 1992, Brisigotti et al. officially named this unique type of renal tumor as MA, which was characterized by an unusual degree of differentiation and cell maturity and somewhat different from nephroblastoma via comparing one hundred childhood nephritic tumors (9). What's more, Davis et al. summarized the clinicopathological characteristics of MA for the first time by retrospectively analyzing 50 cases (3). He found MA mainly occurred in females by well over 2:1 to males and were always unilateral, varying in size, well defined, noninvasive and might be associated with hemorrhage, cystic degeneration, and necrosis (3). Afterwards, accumulating cases were constantly reported from worldwide, providing us with profounder insights of this rare benign tumor (10-12). Nevertheless, the pathogenesis of MA remains unknown. Brown et al. found frequent chromosome 7 and 17 gain and sex chromosome loss by fluorescence in situ hybridization (FISH) analysis of MA, which might lead to genetic susceptibility (13).



**Figure 4** Representative histopathology findings of the resected specimen of MA. Cell morphology of tumor was uniform, with little eosinophilic cytoplasm and non-prominent nucleoli (A,B) and showed tubular and acinar architecture, leading to the formation of glomerular-like or bud-like structures (C,D). HE staining, (A,C)  $\times$ 40, (B,D)  $\times$ 100. MA, metanephric adenoma.

In addition, Choueiri *et al.* identified that BRAF V600E mutations are present in approximately 90% of all MA cases, which might serve as a promising diagnostic tool in the differential diagnosis of renal masses undergoing a percutaneous biopsy (14).

Despite that most MA cases were asymptomatic and accidentally found during physical examination, other potential symptoms of MA primarily included pain, hematuria, palpable mass (15). Besides, a higher incidence of polycythemia was reported in MA than in other renal tumor (16). All patients in our study were admitted to hospital by incidentally inspection other than one case who was accompanied with urologic calculi and hydronephrosis in the ipsilateral renal showed acute pain.

Ultrasound as the preferred check in urologic disease is essential for early detection of various renal tumor, although it can only roughly define the size, and whether the mass is solid or cystic (17). Further CT scan is the main imaging method for the diagnosis of MA. Plain CT usually shows an identical density of MA to the normal renal parenchyma. While in dynamic contrast-enhanced CT, the tumors are found to be slightly enhanced in the renal cortex, renal parenchymal, and pelvic phases and the enhanced degree is significantly lower than that of the normal renal parenchyma. Due to lack of blood supply, MA can be efficiently discriminate from the most common renal clear cell carcinoma which has an abundant blood supply and the enhancement pattern of rapid rise-rapid fall (4). However, it cannot be efficiently differentiated between MA and PRCC or WT by CT imaging. The typical MRI finding of MA is hypointense on T1WI and T2WI, which is not superior to enhanced CT and as a result, it is not imperative to perform a MRI examination (18). Only two cases in our study conducted MRI examination, but the images were unavailable. Overall in imaging manifestations, it is difficult to differentiate MA from some malignant renal tumor like WT or PRCC, which lead to limitation of preoperative diagnosis.

In this study, seven cases underwent LPN and showed no significant complication after surgery. A 22-year-old female and a 30-year-old female underwent LRN, respectively due to the huge size of tumor ( $6 \text{ cm} \times 7 \text{ cm} \times 6.1 \text{ cm}$ ) and a diseased kidney with severe hydronephrosis due to renal calculi. Another patient underwent LRN because the

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CT scan showed unclear boundaries of the tumor versus normal tissue, which suggested the malignancy potential of the tumor, as well as markedly atrophic kidney. No severe complications were observed in all patients. Besides, we carried out closely follow-up for these MA patients, and they all showed good prognoses with no recurrence or metastasis. Therefore, LPN is the pre-dominant surgical procedure to resect this benign tumor.

Postoperative histopathology and immunohistochemistry are most reliable methods for definite diagnosis of MA. In histopathology, these tumors are composed of small epithelial cells that form very small acini in an acellular stroma and also may form tubular, glomeruloid, or polypoid and papillary formations in a few cases (6,19). There is a certain rate of misdiagnosis of MA, because it is phenotypically similar to nephroblastoma and PRCC. In our study, postoperative routine pathology confirmed seven cases were MA, while two cases were misdiagnosed with PRCC and another was misdiagnosed with WT. More reliable diagnosis is depending on the further immunohistochemistry staining. In our cases, immunohistochemistry staining showed that neoplastic cells were always positive for WT-1, Vimentin, Ckpan, Pax-8 and E-Cadherin while negative for NSE, CK7, CD10, EMA and AMACR. The results revealed some differences from previously reported results, which reported that EMA was positive in MA (20). Positive WT-1 and CD57, as well as negative CK7 and AMACR are characterized marks of MA (21). However, two cases exhibited a discordant immunophenotyped: one was negative for WT-1, another was positive for CK7. Therefore, it is necessary to combine the histological structure and the results of immunohistochemistry for the diagnosis of MA. Recently, some scholars identified new potential biomarkers of MA such as BRAF V600E mutation (22). Ding et al. found that BRAF mutation was most frequent in thirty-six MA cases by next-generation DNA sequencing, and the BRAF V600E mutation also appeared in the MA cases, which was rare in other common renal tumors (23). As a result, emerging technologic would bring about more efficient diagnostic approach for MA.

It remains controversial whether performing a renal needle biopsy is necessary before operation. Blanco *et al.* suggested that preoperative recognition of MA by renal needle biopsy allowing for more conservative management, including partial nephrectomies or radiofrequency ablation (24). However, Guo *et al.* disapproved of preoperative biopsy because they thought it could lead to additional risk of tumor spread and bleeding, and could not change the surgical approach or planning whether MA or other malignancy (25). In our study, renal needle biopsy was applied in two cases and both suggested MA, whereas it could not entirely exclude the possibility of WT. The first patient who had biopsy is that 30-year-old women who suffered from acute flank pain and severe hydronephrosis caused by renal stone. Considering the patient was so young, we were going to gain more evidence about the tumorous type through preoperative biopsy to decide whether to perform LPN or not. But the patient herself finally gave up the choice of LPN. The other patient was the 67-year-old women whose CT scan showed unclear boundaries of the tumor versus normal tissue, which suggested the malignancy potential of the tumor, as well as markedly atrophic kidney. We did the biopsy for her to get more pathological evidence to choose LPN or not. But eventually, according to comprehensive judgement and to respect the patients' wishes, both the two patients accepted LRP. While through preoperative biopsy, we can sometimes acquire basis for conservative treatment in selected patients.

Overall, MA is an extremely rare benign tumor which is worthy to report. However, surgery is inevitable due to the undefined preoperative diagnosis, or huge volume which might lead to compression of the renal parenchyma and the potential risk of internal necrosis. Fortunately, the prognosis of MA is optimistic. Nevertheless, more accurate diagnosis is helpful for the nephron sparing to a great extent. To a certain degree, several limitations of this paper should be considered. Firstly, the number of cases included in this study was limited. Meanwhile, the patients were regionally concentrated in the Jiangsu province of China. Therefore, more experience from peers from different areas and Medical Institutions will be helpful to the diagnosis and management of MA and to distinguish it from malignancies of the kidney.

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