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FULL PAPER

CT imaging spectrum and the histopathological features of adult metanephric adenoma

¹G LI, MD, ²F FU, MD, ¹H SONG, PhD, ¹Y NIU, MD and ³Y SU, MD

¹Department of Urology, The second Hospital of Tianjin Medical University, Tianjin Institute of Urology, Tianjin, China

²Department of Radiology, The People's Hospital of Bin Zhou, Bin Zhou, China

³Department of Urology, Tianjin Union Medicine Center, Tianjin, China

Address correspondence to: Dr YanHui Su

E-mail: 690511471@qq.com

Objective: To retrospectively evaluate the radiopathological features of adult metanephric adenoma (MA) and explore whether MA can be differentiated on CT images, including the basis of their morphological features and enhancement patterns.

Methods: 18 consecutive MA cases (age range, 18–66 years; 9 males and 9 females) were pathologically proven and recruited in our study between January 2004 and June 2014. Unenhanced and contrast-enhanced CT were performed and correlated with corresponding pathological findings to differentiate between MA and other renal tumours. The enhancement pattern, lesion contour and presence of calcifications were evaluated.

Results: On unenhanced CT scan, the most common ($n=15$, 83.3%) CT imaging characteristics were the presence of homogeneity and well-defined solid renal masses; the minority ($n=3$, 16.7%) were heterogeneous

or centrally located low-attenuation masses. Contrast-enhanced CT image revealed hypoattenuating heterogeneous masses with varying degrees of contrast enhancement in 16 (88.9%) cases, in contrast to those without increased attenuation in 2 (11.1%) cases. Scattered calcification was found only in one case (5.6%). Pathological results revealed that a total of 6 (33.3%) cases had concomitant malignant carcinoma components; 2 (11.1%) patients had malignant MA; and pure MA was found in 10 cases, with a surprisingly high proportion of malignant tumours.

Conclusion: The positive-predictive values of “high” enhancement seemed relatively characteristic for the diagnosis of malignant and composite MA.

Advances in knowledge: Radiopathological features of adult MA and exploring whether MA can be differentiated on CT images, including the basis of their morphological features and enhancement patterns.

Metanephric adenoma (MA) was first identified in 1979 and has been subsequently classified within the group of metanephric tumours, which comprise MAs, metanephric adenofibromas and metanephric stromal tumours.¹ The wide use of ultrasound, CT and MRI has led to an increase of incidentally discovered renal masses, including benign and malignant renal tumours. However, there are no unique and reliable radiological features for the differentiation of MA from renal cell carcinoma (RCC) and other benign renal tumours except for angioliomyolipoma. There are no well-admitted criteria so this makes a diagnosis difficult; therefore, we performed the investigation focusing on CT imaging characteristics and corresponding pathological findings in order to establish CT diagnostic criteria of MA as the reference standard.

METHODS AND MATERIALS

Design and patients

The clinical and radiological data were retrieved from archival files and were retrospectively analysed. Our institutional review

board of The Second Hospital of Tianjin Medical University and Tianjin Union Medicine Center approved this study and waived the informed consent requirement. Data collected included age, gender, clinical presentation, pre-operative tumour characteristics (size, location, diameter, nearness to collecting system, growth pattern etc) and final pathological findings. In total, 18 patients (9 males and 9 females; mean age, 50 years; range, 18–66 years) between January 2004 and June 2014 in our institutes were enrolled in the investigation.

All cases underwent radical nephrectomy or partial nephrectomy. Two individual radiologists were blinded to any clinical or pathological findings and evaluated the CT images retrospectively. Clinical presentation was incidental to abdominal imaging performed in nine patients; gross haematuria in five patients; and pain or discomfort in four patients. Details of patients' demographic, clinical and pathological data are listed in [Table 1](#). Abdominal biphasic

CT scans (unenhanced, corticomedullary and excretory phase scans) were performed in 4 cases before May 2008; 3-phase contrast-enhanced CT scans were performed in the other 14 patients after May 2008; and corticomedullary phase was available for all CT studies (nephrographic phase was not available in abdominal biphasic CT scan before May 2008). We performed feature analysis and quantitative attenuation measurements for all cases and also measured enhancement in corticomedullary phase. The presence of calcification, tumour-spreading patterns, lymphadenopathy and difference of enhancement pattern (homogeneous, heterogeneous) were all recorded and analysed retrospectively (Table 2).

Statistical analysis

All reported non-parametric statistics *p*-values were two sided and statistical significance was set at $p < 0.05$; the ratio was compared among the two groups by using *t* tests. All data were analysed using SPSS® v. 17 (SPSS Inc., Chicago, IL).

Unenhanced CT image

The imaging characteristics were retrospectively classified and analysed according to tumour diameter, cystic–solid components, calcification, local enlarged lymph nodes, growth pattern, interface with parenchyma, necrosis and tumour attenuation parameters (smaller lesions were excluded because of partial volume effects) on unenhanced and enhanced CT scans. Tumours were classified into homogeneous CT value (isodense), hypoattenuation value

(hypodense) and hyperattenuating value (hyperdense) compared with adjacent normal renal parenchymal on unenhanced CT scan. The pattern of growth was classified into well-demarcated (well circumscribed renal lesions) and ill-demarcated (irregular margin) subtypes. The maximal diameter and size of each lesion were measured on axial images by use of a single linear measurement method.

Contrast-enhanced CT image

Enhancement was defined as increased attenuation in nephrographic phase with a threshold of at least 10 HU; the enhancement pattern was categorized as “slight” (10–30 HU), “high” (>30 HU) and “no” enhancement (≤ 10 HU) compared with unenhanced CT scan. Another classification pattern was homogeneous or heterogeneous enhancement.

RESULTS

Pathological findings

Grossly, MA tends to exhibit a homogeneous cut surface without haemorrhage or necrosis and a solid growth pattern at pathological examination. The cut surface of the tumour displays a yellowish-white or grey colour, and most tumours generally form well-circumscribed encapsulated masses with solid or cystic material. Microscopically, tumours are composed of variable proportions of cells proliferating with the formation of small glomeruloid bodies (Figure 1). Tumour cells have uniformly small and indistinct nucleoli, and scanty cytoplasm. Immunohistochemical staining

Table 1. Clinical and pathological characteristics of metanephric adenoma (MA)

Number	Sex/age (years)	Symptoms	Dimension (cm)	Treatment modality	Pathology diagnosis	Recurrence or metastasis
1	F/48	No	1.4 × 1.5 × 1.5	NSS	MA	No
2	F/65	No	2.5 × 2.5 × 3	RN	MA	No
3	M/62	Haematuria	5 × 6.2 × 4.4	RN	MA	No
4	M/45	Haematuria	3.6 × 3 × 4	RN	MA, PT	No
5	F/33	No	2 × 1.5 × 1.5	NSS	MA	No
6	F/64	No	4.5 × 4 × 4	RN	MA	No
7	F/53	Haematuria	6.5 × 6 × 6	RN	MA, PT	No
8	M/64	No	6 × 3.5 × 5.5	RN	MA	No
9	F/38	No	5 × 4 × 4	RN	MA	No
10	M/65	No	2.7 × 2.5 × 2	NSS	MA, adenocarcinoma	No
11	F/50	Loin pain, haematuria	9 × 8 × 8	RN	MA, chromophobe cell carcinoma	No
12	M/50	No	4 × 4.3 × 3.5	RN	MA	No
13	F/38	No	3 × 2.3 × 3.5	NSS	Malignant	No
14	M/33	No	3 × 2.5 × 2.5	RN	MA	No
15	F/47	No	4.7 × 4 × 4	RN	MA, oncocytic carcinoma	No
16	M/43	No	4 × 3.5 × 3.5	RN	Malignant	No
17	M/51	No	3 × 2.2 × 3	RN	MA, PT	No
18	M/18	No	5.3 × 3.7 × 5	RN	MA	No

F, female; M, male; NSS, nephron-sparing surgery; PT, papillary tumour; RN, radical nephrectomy.

Table 2. The CT characteristics and findings of metanephric adenoma (MA)

Number	Side	Tumour size (cm)	Unenhanced/enhanced attenuation (Hu)	Enhanced pattern	CT findings	
					Growth pattern	Density
1	L	2 × 1.5 × 1.5	37/61	Slight	Well demarcated	Isodense, solid
2	L	2.5 × 2.5 × 3	30/87	High	Ill defined	Isodense, solid
3	R	5 × 6.2 × 4.4	9/12	No	Well demarcated	Hypodense, cystic–solid
4	L	3.6 × 3.0 × 4	21/42	Slight	Ill demarcated	Hypodense, solid
5	R	2 × 1.5 × 1.5	20/25	No	Well demarcated	Hypodense, cystic–solid
6	L	4.5 × 4 × 4	30/46	Slight	Well defined	Isodense, solid, scattered calcification
7	R	6.5 × 6 × 6	36/58	Slight	Ill demarcated	Isodense, solid
8	R	6 × 3.5 × 5.5	45/71	Slight	Ill demarcated	Hyperdense, solid
9	L	5 × 4 × 4	46/107	High	Well demarcated	Isodense, solid, enlarged lymph node
10	R	2.7 × 2.2 × 2	43/51	Slight	Ill demarcated	Isodense, cystic–solid
11	R	9 × 8 × 8	20/58	High	Ill demarcated	Hypodense, solid
12	L	4 × 4.3 × 3.5	25/53	Slight	Well demarcated	Hypodense, cystic–solid
13	L	3 × 2.3 × 3.5	25/30	No	Well demarcated	Hypodense, cystic–solid
14	L	2.8 × 3.5 × 3.5	24/58	High	Well demarcated	Isodense, solid
15	R	4.7 × 4 × 4	33/76	High	Well demarcated	Isodense, solid
16	L	4 × 3.5 × 3.5	26/64	High	Ill demarcated	Hypodense, cystic–solid
17	L	3 × 2.2 × 3	28/34	No	Well demarcated	Isodense, solid
18	R	5.3 × 3.7 × 5	32/46	Slight	Well demarcated	Isodense, solid

L, left; R, right.

showed that most tumour cells were positive for MIB-1, and Vimentin, EMA and CK7 staining were focal and showed weak positivity. In rare cases, tumour cells were composed of epithelial elements and lacked typical architecture of tubules and glomeruloid bodies, and atypia and mitotic activity were present (Figure 2). Composite tumours with foci of malignant tumour cells were found in six cases, including papillary tumours ($n = 3$), oncocytic carcinoma ($n = 1$), adenocarcinoma ($n = 1$) and chromophobe cell carcinoma ($n = 1$). According to the cellular and pathological findings, all 18 cases can be divided into 3 subtypes, including classical MA ($n = 10$), malignant MA ($n = 2$) and composite MA with coexistence of different malignant components ($n = 6$).

Furthermore, in order to compare whether there was radiological difference between malignant and pure MA cases, we classified 18 cases into either Group 1 (pure MA, $n = 10$) or Group 2 (composite and malignant MA, $n = 8$) subjectively.

Radiological findings

In our series, transverse unenhanced CT findings were variable; all cases were round or elliptical in shape and with well-defined margins and a median diameter of 3.9 cm (range, 1.4–9.0 cm). Radiologically, the mean diameter was 3.7 ± 1.6 cm in Group 1; by contrast, the diameter was 4.1 ± 0.8 cm in Group 2. Statistically, there was no significant difference between the two groups

($p > 0.05$). Tumours were located entirely within the renal parenchyma in 3 cases, and 15 cases demonstrated an exophytic pattern, which was located at the periphery of the kidney cortex without involvement of the renal collecting system. Tumours with uniform density (isodense) were found in 10 cases, heterogeneous density in 8 cases including cystic density ($n = 1$), peripheral isodense and central hypodense ($n = 6$), hyperdense ($n = 1$).

As for tumour-spreading patterns, well-demarcated ($n = 10$) and ill-defined ($n = 8$) tumours were found individually. Enlarged lymph node and marked mottling calcification were seen in one case (Figure 3a) with mild enhancement in post-intravenous (i.v.) contrast image (Figure 3b). Cystic and solid lesions were found in larger cases, while a predominantly cystic lesion was found in only one case (Figure 4a) without enhancement in post-i.v. contrast image (Figure 4b). Median CT attenuation values on unenhanced and enhanced scans (mean nephrographic phase attenuation) were 39 HU (27–45 HU) and 63 HU (50–77 HU), respectively. Distinct capsules surrounding the tumour in expansile or exophytic small solid masses were found in 10 patients. According to our pre-supposed post-contrast criterion, enhanced CT scan (nephrographic phase attenuation) revealed “slight” enhancement in nine (50%) cases (Figure 5a,b), lesions without enhancement in three (16.7%) cases (Figure 6a,b) and “high” enhancement in six (33.3%) cases

Figure 1. Microscopic examination of the tumour shows variable proportions of cells proliferating with the formation of small glomeruloid bodies (haematoxylin and eosin staining, original magnification $\times 200$).

(Figure 7a,b). No significant correlation was found between malignant and benign MA in unenhanced CT imaging ($p > 0.05$). The degree of enhancement is the most valuable parameter to predict and identify subtypes of MA. Slight enhancement was 60% in Group 1, in contrast to 37.5% in Group 2 ($p > 0.05$). High enhancement was 20% in Group 1, in contrast to 50% in Group 2 ($p < 0.05$). The positive-predictive values of “high” enhancement for the diagnosis of malignant and composite MA seemed relatively characteristic.

Radiological and pathological correlation

We presumed that different enhancement patterns of MA may be supported by pathological subtype findings, so we sought to determine whether enhancement CT could help differentiate MA from other renal tumours, especially RCC. According to microscopic findings, MA can be divided into three subtypes, as mentioned above. Among them, there were two malignant MA cases and six composite tumours containing foci of malignant components. Given these factors, we proposed the hypothesis that different enhancement may be related to high nuclear-to-cytoplasmic ratio or malignant components, and therefore, the pathological findings may correlate with radiological features and present clues to elucidate the different pathogenesis of CT attenuation values and features. In our cases, one lesion had a higher attenuation value than did renal parenchyma, such hyperattenuation is considered to be related to proteinaceous fluid, a densely packed cellular component. Furthermore, we explored whether MA subtypes were reclassified based on CT attenuation value, tumour-spreading pattern and enhancement pattern, which are the most valuable parameters. Statistical analysis revealed that all tumours were solid with distinct encapsulation and regular margins in Group 1; nine (90%) cases typically appear hypovascular, homogeneous and slightly enhanced after administration of contrast agent, and this characteristic

was in correlation with histopathological findings of papillary or glomeruloid bodies architecture with areas of solid appearance. In the papillary areas, there were frequent psammoma bodies and cells with bland nuclei lining papillae. Radiologically, calcification in renal masses indicated malignancy that was not found in our series except in one benign MA with dotted calcification. In Group 2, six lesions were solid or cystic-solid with regular margins or well-defined growth patterns on unenhanced CT scan. On contrast enhancement, four cases revealed “mild” heterogeneous or circumferential enhancement with low intralésional attenuation, which correlated well with the presence of malignant components occurring in portions of the mass (4/8, 50%). Malignant tumours especial vascular cases correlated with “mild” enhancement pattern. However, our data indicated that pathological features fail to ideally explain the rest of the 50% cases where radiological findings were similar to Group 1. No individual CT criterion was of substantial help in differentiating malignant from benign lesions. Among three distinct enhancement patterns, “mild” ($n = 4$), “high” ($n = 2$) and “slight” ($n = 12$), 50% “mild” cases were found to be mixed with malignant components and were a relatively reliable indicator of malignant cases. In Group 1 ($n = 10$), eight (80%) cases revealed slight enhancements, whereas two (20%) cases showed high enhancements. In Group 2 ($n = 8$), “mild” cases accounted for 50% and its pathological basis was composite of malignant components, and so “mild” enhancement was a relatively reliable indicator of malignant cases compared with Group 1 ($p < 0.05$). Conventionally, a malignant renal mass is frequently found with irregular margins and larger diameters. However, there was no statistical difference between tumour appearance, diameter and CT value on unenhanced CT scan ($p = 0.03$).

DISCUSSION

MA is a rare benign renal neoplasm that originates in the epithelial cells with an uncertain history. The nomenclature had been confusing until 1988, and it was originally described

Figure 2. Microscopically, tumour cells were composed of epithelial elements and lacked typical architecture of tubules and glomeruloid bodies with atypical and mitotic activity (haematoxylin and eosin staining, original magnification $\times 400$).

Figure 3. Axial abdominal CT revealed marked mottling calcification in the right renal parenchyma (a). In post intravenous contrast CT scan, the tumour showed mild enhancement (b). A, anterior; P, posterior.

as MA. No special tumour marker has been reported in the literature, the genetic profile of MA is distinct from papillary RCC and Wilms tumour.² Meanwhile, chromosomal abnormalities are also found in MA;³ the simultaneous presence of *BRAF* gene mutation and 2p deletion play a great role in the pathogenesis of MA.⁴

Pathologically, MA is recognized as a special type of benign renal epithelial tumour that is derived from the metanephric blastema with a favourable prognosis. It makes up approximately 0.2% of all adult renal epithelial neoplasms.⁵ To date, approximately 100 cases of MA have been reported in the English literature.⁶ In rare conditions, composite MA is a coexistence of different renal tumour components such as papillary RCC, Wilms tumour and RCC.^{7,8} In immunohistochemical staining, MA is positive for CD57, Vimentin, WT1 and CK7, and is negative for EMA and S-100. These marker profiles may be useful in differentiating MA from papillary RCC and Wilms tumour.⁹

Clinically, MA seemed to have a distinctive female preponderance; nevertheless, no gender difference was found in our series. Most cases were asymptomatic and were detected incidentally on imaging performed for other indications. Clinical symptoms such as haematuria, palpable mass, flank pain, polycythaemia or chyluria are unspecific.¹⁰ Additionally, it has been reported that MA may be multifocal or bilateral.¹¹

CT, especially dynamic enhancement pattern, was a valuable means of distinguishing MA subtypes; it is anticipated to improve the diagnostic accuracy and reliability. However, little information has been reported with regard to the radiological diagnosis of MA.^{12,13} CT characteristics of MA are unreliable in

differentiating between RCC, there are no well-established, image-based criteria that can be used to diagnose most renal masses definitively. In general opinion, malignant renal masses may be larger and bulky; however, there was no difference in diameter among MA subtype cases ($p > 0.05$). It has been reported that the presence of an angular interface is a strong predictor of a benign tumour with a sensitivity of 78% and a specificity of 100%;¹⁴ meanwhile, the presence of an angular interface does not exclude a malignant tumour. In our series, the presence of angular interface was not significantly associated with benign or malignant tumour. So far, histopathological diagnosis remains the reference standard, and CT may be of substantial help in pre-operative diagnosis. The usefulness of CT for the characterization of MA has not yet been determined. The high attenuation value on unenhanced CT has been reported to be a characteristic finding of MA,¹⁵ it was speculated to be related to the presence of psammomatous calcification and a high nuclear-to-cytoplasmic ratio.¹⁶ Radiologically, pre-operative diagnosis of MA can be problematic owing to no pathognomonic findings, and there was a wide spectrum of neoplastic conditions that needs to be differentiated. It is hard to differentiate MA from RCC based on imaging features. MA typically appears as a well-defined, unencapsulated, solitary solid mass.^{12,16} It commonly appears as equal attenuation with a regular margin on unenhanced CT imaging and of lower attenuation on enhancement CT, which suggests less vascularization. Larger tumours appear as heterogeneous, hypovascular masses with frequent foci of haemorrhage and necrosis.¹⁶ Nevertheless, our findings revealed that there was infrequent haemorrhage or necrosis on radiological and pathological findings. Calcification is reported as a key radiological sign of MA, it occurs more often in MA than in other renal neoplasia.¹ However, there was only one case (5.6%) that

Figure 4. Predominant cystic lesion was found only in one case (a), without enhancement in post intravenous contrast image (b).

Figure 5. Enhanced CT scan (nephrographic phase attenuation) revealed “slight” enhancement (b) compared with pre-intravenous image (a).

revealed calcification in our series. Additionally, only one case (5.6%) was predominantly with the cystic form, which was rarely reported in English literature.¹⁷ In our initial experience, MA is a heterogeneous neoplasm with different pathological and biological characteristics; similar findings include metastatic cases reported in English literature.^{18,19} Theoretically, CT findings, especially enhancement, may reflect the histological composition, and the variable enhancement degree concerning MA should suggest the possibility of coexisting subtypes. Correspondingly, tumour CT attenuation values and enhancement ratios were correlated with histological subtypes. In our series, there were two distinct patterns on cross-sectional images that reflect its pathological appearance. However, few researchers reported that there was a correlation between morphology and imaging pattern.¹⁶

CT remains the standard modality to use in diagnosing and staging of renal neoplasms, and there is a wide spectrum of uncommon non-neoplastic conditions, including tumour-like conditions, that need to be differentiated. Hyperattenuating renal masses on unenhanced CT, especially tumour attenuation value of >74 HU, are significantly correlated with RCC, and lesions with gradual enhancement were more likely to be benign.²⁰ In conventional opinion, massive haemorrhage and necrosis means malignant potential; however, it was not independently associated with malignant histology and also can

be found in MA cases.²¹ It has been reported that about 90% of RCCs are hypervascular tumours with heterogeneous enhancing pattern, 75% of papillary RCCs are hypovascular and homogeneous or peripheral enhancement pattern, most chromophobe tumours demonstrate moderate degrees of enhancement.^{20,22} Nevertheless, it was difficult to differentiate MA from papillary RCC on CT,²³ and the final diagnosis relies on histological and immunohistochemical studies. In our study, it was difficult to pre-operatively predict the possibility of MA by one single parameter, and we attempted to build a multiple-feature predictive model that could be used to differentiate between MA and other renal tumours. A combination of parameters of isodensity, slight enhancement and well-defined margins were more predictive than a single parameter.

There were several limitations in our investigation. First, the retrospective design with limited numbers at a single centre might have introduced patient selection bias, and not all cases were scanned with the same scanning technique of three-phase CT enhancement phase protocol or not all enhancement parameters were analysed in detail. Second, there was lack of objective definitions of different phase-specific attenuation threshold levels that we subjectively evaluated and divided into three enhancement patterns. This pattern should have been normalized using the measured

Figure 6. CT scan revealed lesions without enhancement in post intravenous contrast CT scan (b) compared with pre-intravenous contrast imaging (a).

Figure 7. Axial abdominal CT revealed “high” enhancement (b) in post-intravenous (i.v.) contrast CT scan compared with pre-i.v. contrast imaging (a).

attenuation of the renal cortex phase to ensure that attenuation is independent of technical or patient variability. Third, our findings overlap or are in discord with the results of previous studies; there was a statistical significance in the subtype group that needs to be verified in further and larger research. Even with these limitations, the results of our investigations suggest that there may be a relationship between CT enhancement and MA, especially subtype histological findings.

CONCLUSION

To our knowledge, this is the largest reported CT characterization of MA to date. The imaging features of MA overlap with other renal neoplasms with a variable imaging pattern and lack pathognomonic imaging.

However, we found a difference in enhancement pattern between pure MA and composite MA cases. Combinations of multiple characteristics may be helpful in predicting MA and corresponding subtypes. All radiologists and clinicians should be aware that pre-operative accurate diagnosis is crucial for optimal management. Moreover, further studies are needed to identify and clarify the association between CT and pathological findings.

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