Critical Reviews in Oncology / Hematology 150 (2020) 102970

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Paediatric metanephric tumours: a clinicopathological and molecular characterisation

Dominique V.C. de Jel[a,1], Janna A. Hol[a,*,1], Ariadne H.A.G. Ooms[a,e], Ronald R. de Krijger[a,b], Marjolijn C.J. Jongmans[a,c], Annemieke S. Littooij[a,d], Jarno Drost[a,f], Martine van Grotel[a], Marry M. van den Heuvel-Eibrink[a]

[a] Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands
[b] Department of Pathology, University Medical Center Utrecht (UMCU), Utrecht, The Netherlands
[c] Department of Clinical Genetics, University Medical Center Utrecht (UMCU), Utrecht, The Netherlands
[d] Department of Radiology, University Medical Center Utrecht (UMCU), Utrecht, The Netherlands
[e] Department of Pathology, Pathan, Rotterdam, The Netherlands
[f] Oncode Institute, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

ARTICLE INFO

Keywords:
metanephric
adenoma
adenofibroma
stromal tumour
renal
paediatric

ABSTRACT

To characterize metanephric tumours in children, we performed a literature review investigating paediatric metanephric adenomas (MA), metanephric stromal tumours (MST) and metanephric adenofibromas (MAF). Including two patients from our own institution (MA, MAF), 110 individual cases (41 MA, 20 MAF, 49 MST) were identified. Additionally, fifteen composite tumours were identified, with areas of MA/MAF and Wilms tumour (WT) or papillary carcinoma. No distinct clinical or radiological features could be defined. In pure metanephric tumours, histologically proven distant metastases were reported once (MA), relapse was reported once (MST) and one tumour-related death occurred (MST). Somatic *BRAF*-V600E mutations were tested in 15 cases, and identified in 3/6 MA, 3/3 MAF, and 6/6 MST. In our institution the MA harboured a somatic *KRAS*-G12R mutation. Overall, paediatric metanephric tumours are difficult to discriminate from other renal tumours at presentation, behave relatively benign, and the occurrence of composite tumours warrants analysis of underlying (genetic) pathways.

1. INTRODUCTION

The metanephric tumour family comprises a group of uncommon renal tumours including metanephric adenoma (MA), metanephric stromal tumour (MST) and metanephric adenofibroma (MAF). Two of these entities (MST and MAF) predominantly affect children, while MA typically occurs in the fifth to sixth decade of life.(Argani, 2005) Metanephric tumours are generally unencapsulated tumours, believed to originate from postnatal remnants of metanephric blastema, and cover an epithelial to stromal histological spectrum.(Argani and Beckwith, 2000; Arroyo et al., 2001)

MA has been reported by various terminology, including 'nephrome néphronogène' (Pagès and Granier, 1980), 'persistent renal blastema' (Scharfenberg and Beckman, 1984) and 'embryonal adenoma' (Werbrouck et al., 1990) until the term metanephric adenoma was introduced in 1992.(Brisigotti et al., 1992) MA is a highly cellular tumour exclusively composed of epithelial cells, arranged in closely packed tubules of papillae, often with numerous psammoma bodies. Although it can resemble epithelial Wilms tumour (WT) (Benson et al., 2018; Brisigotti et al., 1992; Kinney et al., 2015), it has more uniform nuclei, finely dispersed chromatin, and lack of mitotic activity and atypia. In contrast to WTs, the majority (~90%) of MAs carry a *BRAF* V600E mutation, which can be demonstrated by the specific *BRAF* V600E immunohistochemical stain.(Chami et al., 2015) If a *BRAF* mutation is absent, diffuse CD57 staining favours the diagnosis of MA, but does not rule out WT. Furthermore, CK7 negativity of WTs and most MAs distinguishes them from papillary renal cell carcinoma.(Kinney et al., 2015)

MST, on the other end of the spectrum, is a stromal tumour. Most reported paediatric MSTs were initially classified as congenital mesoblastic nephromas (CMN) until MST was recognized as a separate entity by Beckwith et al.(Beckwith et al., 1998) In contrast to clear cell

* Corresponding author at: Princess Máxima Center for Pediatric Oncology, Heidelberglaan 25, 3584CS, Utrecht, The Netherlands.
E-mail address: j.hol@prinsesmaximacentrum.nl (J.A. Hol).
[1] Authors contributed equally to this work.

https://doi.org/10.1016/j.critrevonc.2020.102970
Received 29 July 2019; Received in revised form 5 February 2020; Accepted 15 April 2020

sarcoma of the kidney (CCSK), congenital mesoblastic nephroma (CMN) and stromal WT, MST is microscopically characterized by spindle cells with alternating areas of hyper- and hypocellularity and subtle infiltration of the adjacent kidney. Moreover, tumour cells in MST often display a concentric arrangement around entrapped tubules, referred to as "onion skinning", and vascular changes of entrapped arterioles (angiodysplasia), and the majority of MSTs are *BRAF* V600E and CD34 positive, while CCSK, CMN and WT are usually negative.(Argani et al., 2000) MST can also show heterologous differentiation such as glial tissue or cartilage.(Argani and Beckwith, 2000; Beckwith, 1998; Kacar et al., 2011; Palese et al., 2001)

MAF was originally referred to as 'nephrogenic adenofibroma' (Guzman et al., 2000; Hennigar and Beckwith, 1992), however, the term metanephric adenofibroma is now used in the WHO classification of renal tumours.(Moch et al., 2016) MAF is a biphasic tumour with an epithelial component similar to MA, and a stromal component similar to MST. These two components can be present in highly variable proportions.(Shek et al., 1999)

Currently, it is not possible to distinguish metanephric tumours from other paediatric renal tumours at presentation, based on clinical characteristics or imaging alone. In this report, we present two paediatric cases of MA and MAF diagnosed in our institution and the results of an extensive literature review, with the aim to characterize clinicopathological and molecular features, and outcome of metanephric tumours in childhood.

2. METHODS

The index patients were diagnosed and treated at the Princess Máxima Center for Pediatric Oncology, and radiology and histopathology were reviewed for this manuscript, in addition to standard histological review according to the SIOP 2001 renal tumour protocol. (Pritchard-Jones et al., 2015) To support the histopathological diagnosis, tumour DNA (≥10 ng extracted from formalin-fixed paraffin embedded tissue) of both patients was sequenced (Ion AmpliSeq™ Cancer Hotspot Panel v2, Thermo Fisher Scientific, Waltham, US). Variants with a variant allele frequency (VAF) ≥5% were reported.

For the literature review, databases of PubMed, Embase and Cochrane were searched. Search details are provided in Supplemental Table 1. The yield of this search was combined and duplicates were removed. All articles were screened based on title and abstract and full texts were evaluated, both by two independent reviewers (DVCdJ and JAH). Cross references check of included articles was performed to identify additional relevant reports.

3. CASE PRESENTATION

3.1. Case 1: Metanephric adenoma

A 21-month-old boy was admitted with a prolonged urinary tract infection (UTI). Abdominal ultrasound and CT-imaging (Fig. 1a) depicted a hyperechoic lobular mass in the lower pole of the left kidney, showing nodular infiltration of the renal cortex. There were no metastases. According to the SIOP 2001 protocol, pre-operative chemotherapy (vincristine and actinomycin-D) was administered for 4 weeks and the tumour volume decreased from 84.9 mL to 29.7 mL. Histological evaluation of the left (radical) nephrectomy specimen (Fig. 1b,c) revealed a metanephric adenoma (MA), based on the presence of a well-demarcated lobular mass composed exclusively of epithelial cells forming papillae and tubules, associated with numerous psammoma bodies, and rare mitotic figures. Microscopically, the tumour had a thin fibrous capsule through which the tumour infiltrated the hilar area at various sites (SIOP stage II). There were no chemotherapy-induced changes. Sequencing of the tumour detected a *KRAS* exon 2 mutation (c.34 G > C; p.Gly12Arg, also known as *KRAS* G12R, VAF 41%) but no mutations in *BRAF*. The family history revealed that the patient's grandmother had died from an unspecified pancreatic tumour as a teenager, but germline genetic tests had not been performed. At last follow-up, three years after diagnosis, the patient was well and there were no signs of recurrence.

3.2. Case 2: Metanephric adenofibroma

A seven-month-old boy presented to the outpatient clinic with a UTI and hypertension (RR 122/77 mmHg, > p95). Abdominal ultrasound and MRI-imaging (Fig. 2a) depicted a hyperechoic mass in the lower pole of the left kidney with nodular infiltration of the adjacent renal tissue and only limited restriction on diffusion-weighted MRI. There were no metastases. The patient was subjected to four weeks of pre-operative chemotherapy as per SIOP 2001 protocol(similar to case 1), but tumour size did not decrease. In week five, left (radical) nephrectomy was performed after which blood pressure normalized. Histologically, a MAF was diagnosed based on the combination of spindle cells (stromal component) and epithelial structures resembling those of a metanephric adenoma (Fig. 2b,c). The tumour was unencapsulated. The epithelial component showed differentiatied epithelial structures (papillae, tubules), with characteristic psammoma bodies, and sparse mitotic figures. Within the spindle cell component, onion skinning and angiodysplasia was present. The spindle cell component infiltrated the pre-existing renal parenchyma and the tumour showed extension along vascular structures and nerves into the hilum, but the resection margins were free (SIOP stage II). On histology, no chemotherapy-induced changes were observed. Sequencing of the tumour detected a mutation in *BRAF* exon 15: c.1779 T > A; p.Val600Glu, also known as *BRAF* V600E (VAF 32%). No germline genetic tests were performed. The patient's monozygotic twin brother was screened by renal ultrasound, which showed no abnormalities, and further family history and follow-up so far (three years) was unremarkable.

4. LITERATURE REVIEW

After removal of duplicates, the literature search yielded 382 articles (Fig. 3). A total of 56 articles were included after screening title/abstract and full text. Three cases were reported more than once; in each case the report with the most detailed documented information was included in the analysis. A total of 110 well-described paediatric cases (Table 1) were identified and summarized, including our two cases: 41 MA (Supplemental Table 2), 20 MAF (Supplemental Table 3) and 49 MST (Supplemental Table 4).

4.1. Clinical characteristics

Median age at presentation was eight-and-a-half years (range: two months - eighteen years) for MA, five years (range: seven months – eleven years) for MAF, and 23 months (range: zero days – fifteen years) for MST (Table 1). Clinical findings and/or symptoms at presentation were available for 90 patients (Table 2). In MA, the most common finding at presentation was polycythaemia, present in 10/34 (30%) cases versus 2/13 (15%) MAF and none of the MST. Six out of 34 MA (18%) and one MAF (14%) were asymptomatic and presented as an incidental finding upon examination for an unrelated condition. For MST, the most common presenting symptom was a visible or palpable mass, which was reported in 19/43 (44%) patients. In MAF presenting symptoms differed widely (Supplemental Table 2-4).

4.2. Disease stage

All identified patients with pure metanephric tumours had unilateral disease. Regional (abdominal) lymph node involvement was described in two MA patients (Renshaw et al., 2000; Yin et al., 2015), however, lymph node sampling was frequently not performed or

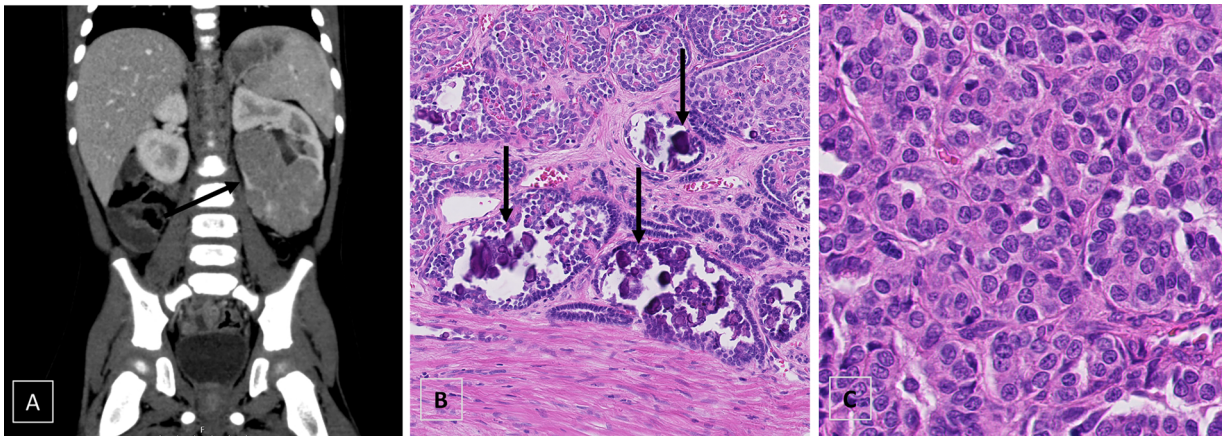

Fig. 1. Radiological and histopathological studies of case 1 (M, 21 months, metanephric adenoma).
1a: Contrast-enhanced abdominal CT, showing a lobular mass in the lower pole of the left kidney. Strands of renal cortical tissue (hyperdense, arrow) are seen in between the tumour nodules.
1b-c: Hematoxylin and eosin stained sections displaying the nodular aspect of the lesion with multiple psammoma bodies (b, arrows). On higher magnification (c), the epithelial nature of the lesion can be appreciated, as well as the lack of mitoses and nuclear atypia, distinguishing it from Wilms tumour.

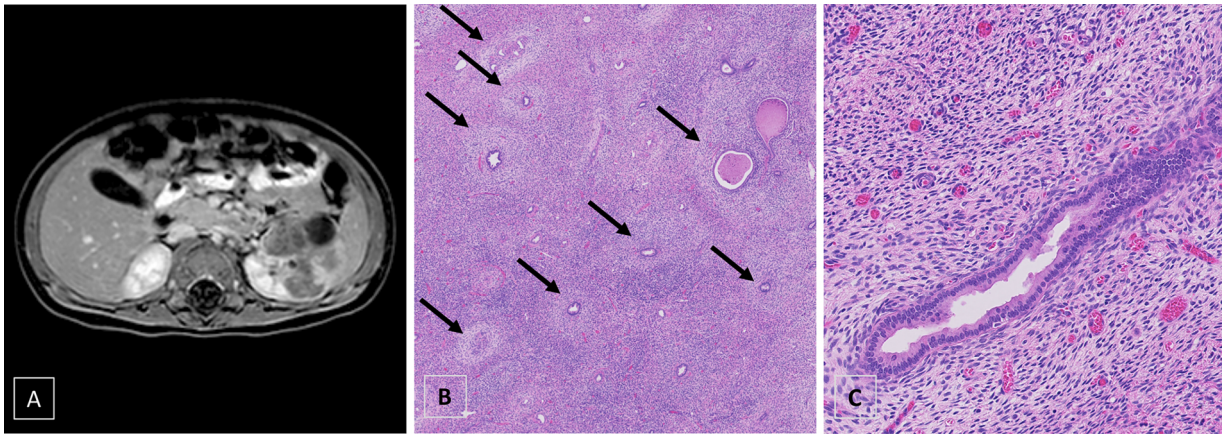

Fig. 2. Radiological and histopathological studies of case 2 (M, 7 months, metaneprhic adenofibroma).
2a: Contrast-enhanced abdominal MRI showing a lobular mass with both cystic and solid components, protruding into the renal cortex.
2b-c: Hematoxylin and eosin- stained sections displaying varying amounts of stromal and epithelial components, with the typical onion-skinning (arrows) around epithelium-lined tubulues. On higher magnification (c), neither component shows atypia or high mitotic activity.

described. Two patients were suspected of having distant metastases at diagnosis, which were histologically confirmed in one of them. This was a patient with tumour spread to para-aortic, hilar, and aortic bifurcation lymph nodes, histologically characterized as MA by Beckwith (Renshaw et al., 2000), but recently reviewed by Argani who favoured a diagnosis of differentiated WT with MA-like areas.(Wobker et al., 2019) The second patient suspected of distant metastases was a patient with MAF who presented with lung metastases on chest CT, but these were not examined histologically and they completely resolved after pre-operative chemotherapy (six weeks AVD).(Raj et al., 2016) Local invasion of the renal pelvis was described in one MA (this report), two MAF (this report, Agarwal et al., 2017), and one MST (De Pasquale et al., 2011).

4.3. Imaging features

In the reviewed literature, metanephric tumours were usually described as hyperechoic and well circumscribed, although cysts, haemorrhage and necrosis were reported. In some cases of MA, calcifications were observed (Bastos Netto et al., 2007; Küpeli et al., 2009a; Saltzman et al., 2017; Zhang et al., 2011) No other distinct patterns could be identified in various imaging modalities.

4.4. Treatment

Treatment of metanephric tumours included complete or partial nephrectomy, with or without pre- and post-operative chemo- or radiotherapy (Table 1). For MA, information regarding treatment was missing in five cases. Among the other 36 MA patients, only two received pre-operative chemotherapy according to SIOP Renal Tumour Study Group (RTSG) protocols.(this report, (Barroca et al., 2016a)) Two patients received post-operative treatment, one because of metastatic MA (Renshaw et al., 2000) and one because of misclassification on histology by local pathology (Comerci et al., 1996). For paediatric MAF, pre-operative chemotherapy was administered in only 3/21 cases. Post-operative treatment was administered in 7/21 patients according to WT protocols, in some cases discontinued after the diagnosis of MAF was confirmed.(Arroyo et al., 2001) Out of 49 patients with MST, only one patient received pre-operative radiotherapy (indication and protocol not specified).(Argani and Beckwith, 2000) Five patients received post-operative treatment, while information on post-operative treatment was missing in six cases. Indications for post-operative treatment were renal pelvis invasion in one case (De Pasquale et al., 2011) and not specified in the other four cases.(Argani and Beckwith, 2000)

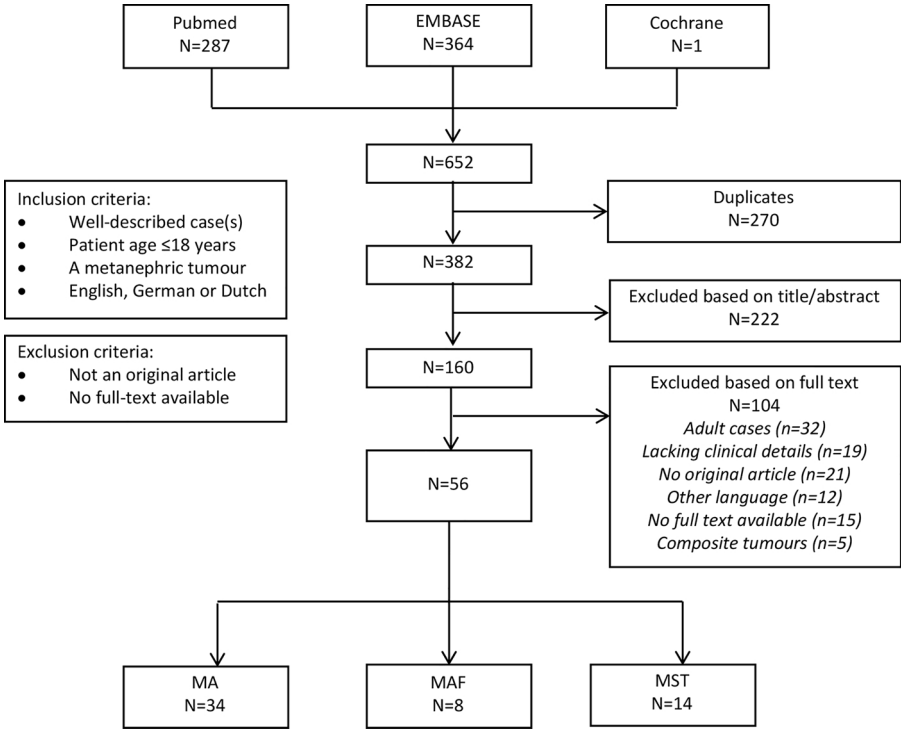

Fig. 3. Flowchart of the literature search (updated December 29th, 2018).
Legend: MA: metanephric adenoma, MAF: metanephric adenofibroma, MST: metanephric stromal tumour, N: number of reports.

4.5. Relapse and survival

Out of the 110 summarized patients, one relapse was reported in a nine-month-old patient with MST. This child was rescued by second surgery with no signs of disease 31 months later.(De Pasquale et al., 2011) This patient had been initially diagnosed with CMN and developed a para-testicular MST six months after completing treatment. At relapse, the initial histological diagnosis was retrospectively reclassified as MST.

One tumour-related death was reported in metanephric tumours, which concerned a neonate with MST who died during surgery due to extensive angiodysplasia.(Argani and Beckwith, 2000) Notably, the literature review showed that angiodysplasia (intra- and extrarenal) had been reported multiple times in MST and MAF, in some cases causing morbidity such as renal artery aneurysms, hypertension or, as demonstrated by this case, intraoperative haemorrhage leading to death.(Argani and Beckwith, 2000)

4.6. Tumour biology

Out of only fifteen paediatric tumours that were assessed for *BRAF* V600E mutations, twelve (80%) tested positive: 3/6 MA, 3/3 MAF and 6/6 MST.(Argani et al., 2016; Barroca et al., 2016b; Chami et al., 2015; Mangray et al., 2015; Yin et al., 2015) Exact variant allele frequencies were not reported and 2/12 *BRAF* V600E mutations were detected by immunostaining alone.

Other somatic mutations, such as the *KRAS* G12R mutation detected in our case 1, were not identified or assessed in the reviewed literature. Structural chromosomal variation was assessed using FISH or karyotype analysis in eight MA (Burger et al., 2007; Drut et al., 2001; Kinney et al., 2015; Kohashi et al., 2009; Konety et al., 1998; Rakheja et al., 2005; Renshaw et al., 2000; Yoshioka et al., 2007), showing a balanced t(9;15)(p24;q24) and inv(12)(q13q15) in one case.(Drut et al., 2001; Rakheja et al., 2005) In the two reports that described cytogenetic studies in MAF, a trisomy 11 was found.(Arroyo et al., 2001; Guzman et al., 2000) Structural chromosomal variants were not described in MST.

No germline mutations have been reported in children with metanephric tumours. One case report described a six-year-old girl with hemihypertrophy in whom MA was diagnosed.(Küpeli et al., 2009b) Another report described MA in a 5-year-old boy with ipsilateral giant congenital nevus, leg length discrepancy and undescended testis. However, in neither of these cases genetic testing was performed. (McNeil et al., 2008)

4.7. Composite or metachronous tumours

In addition to the 110 patients reviewed in the previous paragraphs, eighteen patients ≤18 years were reported to have composite or metachronous tumours, including MA (five cases) or MAF (thirteen cases) in combination with other tumour types. Pasricha et al. reported a four-year-old boy with bilateral MA (right-sided multicentric MA) with left-sided WT. Adjacent to the left-sided WT, a microscopic lesion was identified with similar morphology to that of the right-sided MA. In contrast to the epithelial component of the WT, immunohistochemical staining of this lesion was positive for vimentin and CD57, and negative for EMA.(Pasricha et al., 2012)

Recently, Wobker et al. described eleven "MA-epithelial WT overlap lesions". Three of these lesions occurred in children, including a three-year-old boy, a three-year-old girl and a six-year-old boy. All three tumours were predominantly epithelial WT that demonstrated focal better-differentiated tubular areas with diminished mitotic activity, resembling MA. Two of the three lesions tested positive for the *BRAF* V600E mutation.(Wobker et al., 2019)

In the fifth case of composite MA, an eleven-year-old girl, one area in the tumour was consistent with MA. However, another area was characteristic for papillary carcinoma with larger nuclei and small but evident nucleoli and immunohistochemically positive for CEA and keratin 7 (while both were negative in the MA component). FISH revealed trisomy of the centromeric region of chromosome 17, whereas there was disomy of this region in the MA component.(Drut et al., 2001)

Arroyo et al. described seven paediatric cases of composite MAF/

Table 1
Summary of identified cases in this literature review on metanephric adenoma (MA), metanephric adenofibroma (MAF) and metanephric stromal tumour (MST) in patients ≤ 18 years. *See supplemental material for full literature tables per tumour type.*

Tumour type	N	Age Median in months (range)	Sex M	Sex F	Sex NA	Stage Renal pelvis invasion	Lymph node involvement	Distant metastases	Treatment Pe-operative treatment	Radical nephrectomy	Partial nephrectomy	Post-operative treatment	Histopathology and mutation status in tumour tissue	Outcome Relapse	Outcome Death	Median duration of FU
MA	41	102 (2-222)	20	21	-	1	2	-	2 CT	18 *5 NA*	19	2 CT +/- RT *5 NA*	3/6 BRAF V600E+ *Novel KRAS G12R mutation (N = 1)*	-	-	6 months
MAF	20	36 (7-144)	9	10	1	2	-	1	3 CT	18	2	7 CT	3/3 BRAF V600E+	-	-	6 months
MST	49	23 (0-186)	28	19	2	1	-	-	1 CT	46 *1 no surgery*	2	5 CT +/- 3 RT *6 NA*	6/6 BRAF V600E+	1	1	14 months
Total	110	42 (0-222)	57	50	3	4	2	1	4	83 *5 NA*	23	17 CT 5 RT *11 NA*	12/15 BRAF V600E+	1	1	8 months

Legend: MA: metanephric adenoma, MAF: metanephric adenofibroma, MST: metanephric stromal tumour, M: male, F: female, NA: not available, FU: follow-up, CT: chemotherapy, RT: radiotherapy, N: number of patients.

WT and three of composite MAF and tubulopapillary carcinoma. (Arroyo et al., 2001) The composite MAF/WT tumours all contained a dominant nodule with features of epithelial-predominant WT, while MAF stroma was present at the periphery of the lesion, intermingled with the native kidney. In the three composite MAF/carcinoma cases, the MAF component contained nodules of epithelial proliferation characterized by vesicular nuclei and abundant eosinophilic cytoplasm.

A composite MAF and papillary carcinoma was also described by Chami et al.(Chami et al., 2015) Unlike the MAF component, the carcinoma component showed diffuse positivity for CK7, EMA and CD10. Both components stained diffusely positive for the *BRAF* V600E mutation and showed normal copy numbers for the tested FISH probes.

Finally, Galuzzo et al. described an eighteen-year-old patient with a complex tumour containing areas of MAF, WT and papillary carcinoma. All components showed characteristic immunohistochemical features for its specific histological subtype, with the renal cell carcinoma displaying an extensive undifferentiated component. This patient died two months after surgery due to lung metastases and a local relapse with tumour dissemination throughout the abdominal cavity (no autopsy performed).(Galluzzo et al., 2012) Paediatric MST has never been described in combination with other tumour types.

5. DISCUSSION

As shown by this literature review, differentiating paediatric metanephric tumours from other renal tumours is difficult based on clinical presentation and (even DWI-MRI-)imaging alone, and even the histopathological assessment can be challenging. Clinically, polycythaemia at presentation in a child with a renal tumour could point clinicians towards the diagnosis of MA or MAF. Polycythaemia, a common finding in adults with MA, is a rare paraneoplastic syndrome thought to arise from erythropoietin production by the tumour.(Davis et al., 1995) It is only rarely observed in WT and RCC.(Argani, 2005)

Radiologically, metanephric tumours were usually described as well-demarcated and hyperechoic. In some cases of MA calcifications were reported (although not a unique feature of MA). In our two cases both tumours showed nodular infiltration of the adjacent renal cortex, and in case 2 a lack of diffusion restriction was seen on diffusion-weighted MRI.(Agarwal, 2017) Overall, histopathological evaluation of the complete nephrectomy specimen remains crucial for the diagnosis.

Outcome of metanephric tumours appears to be favourable, although follow-up data were limited in most reports. Histologically proven distant lymph node metastases were only reported once in MA, which, after review of the slides, may represent a case of differentiated WT mimicking MA. Lung metastases were radiologically suspected in one MAF but not histologically proven. Relapse and mortality did not occur in the reviewed literature on paediatric MA and MAF. In children with MST, relapse was only reported once, successfully treated with resurgery, and one death was reported in another case of MST due to extensive angiodysplasia.

Metanephric tumours can occur as composite tumours with areas of RCC and WT. This may suggest that metanephric tumours share a common origin with WT and RCC.(Argani, 2005; Arroyo et al., 2001; Wobker et al., 2019) Composite tumours encountered in this review included MAF with WT and/or RCC, MA with WT or papillary RCC and one bilateral case of MA with contralateral WT. In the report by Arroyo et al., patients with combined MAF and RCC tended to be older than patients with usual MAF.(Arroyo et al., 2001) The authors hypothesize that papillary RCC may be a late event in MAF, which remains asymptomatic during childhood.(Arroyo et al., 2001) WT on the other hand, may mature into a metanephric tumour, suggesting metanephric tumours represent the fully differentiated end of the WT spectrum. (Argani, 2005) Alternatively, as suggested by Wobker et al., MA may also have the ability to undergo malignant transformation and develop into (epithelial) WT. This hypothesis seems to be supported by the identification of mitotic activity in some MA, and by the five adult WT

Table 2
Summary of clinical findings/symptoms at presentation in this literature review (available for 92 cases), N (%).

Tumour type	N	Asymptomatic	Polycythaemia	Visible/palpable abdominal mass	Haematuria	Flank or abdominal pain	Urinary tract infection	Gastro-intestinal complaints	Other
MA	34	6 (18%)	10 (30%)	2 (6%)	5 (15%)	6 (18%)	4 (12%)	2 (6%)	7 (21%)
MAF	13	1 (8%)	2 (15%)	1 (8%)	6 (46%)	1 (8%)	3 (20%)	0 (-)	0 (-)
MST	43	6 (14%)	0 (-)	19 (44%)	5 (12%)	6 (14%)	3 (7%)	0 (-)	6 (14%)
Total	90	13 (14%)	12 (13%)	22 (24%)	16 (18%)	13 (14%)	10 (11%)	2 (2%)	13 (14%)

Legend: MA: metanephric adenoma, MAF: metanephric adenofibroma, MST: metanephric stromal tumour, N: number of patients.

cases with areas resembling MA, described in Wobker et al. 2019. (Wobker et al., 2019) So far, composite tumours have not been observed in children with MST, although MST does morphologically mimic intralobar nephrogenic rests, one of the precursors of WT. (Argani, 2005)

The *BRAF* V600E mutation is the most common somatic mutation in metanephric tumours and is identified in ~90% of MA in adult patients.(Chami et al., 2015; Choueiri et al., 2012) In our review, only a few paediatric metanephric tumours were tested for this mutation, of which all but three cases tested positive.(Argani et al., 2016; Barroca et al., 2016; Chami et al., 2015; Mangray et al., 2015; Yin et al., 2015) A recent study by Marsden et al. was not included in this review because it lacked clinical details, but described *BRAF* V600E testing in seventeen paediatric MST, showing that 11/17 (64%) harboured the mutation. (Marsden et al., 2017) Interestingly, in one of the composite tumours, the areas of MAF and papillary carcinoma were found to be genetically related by the same *BRAF* V600E mutation.(Chami et al., 2015) Recently, the *BRAF* V600 mutation was also identified in two paediatric and two adult cases of epithelial WT, with areas resembling MA, where it was demonstrated in both components.(Wobker et al., 2019)

The identified *KRAS* exon 2 mutation (*KRAS* G12R*)* in the MA of our case 1, has not been reported in metanephric tumours before. A different *KRAS* mutation (*KRAS* G12D*)* was recently identified in a WT. (Polosukhina et al., 2017) *KRAS* is a component of the same MAPK/ERK-pathway as *BRAF*, in which *BRAF* is the downstream effector of *KRAS*. Both *KRAS* and *BRAF* mutations are considered genetic drivers of cancer and are highly prevalent in tumours with a poor prognosis, although mutations and/or rearrangements in these genes are increasingly identified in benign lesions, including congenital mesoblastic nephroma in the kidney.(Wegert et al., 2018) This suggests that the impact of these mutations on malignant transformation may be dependent on context and timing.(Kato et al., 2003)

6. CONCLUSION

Metanephric tumours of the kidney (MA, MAF and MST) are rare tumours, of which MAF and MST occur primarily in children. At presentation, they can be difficult to distinguish from other renal tumours, although ancillary techniques aid in reaching the correct diagnosis. While outcome after nephrectomy is favourable, the occurrence of composite tumours, with areas resembling WT or papillary renal cell carcinoma, warrants further analysis of underlying (genetic) pathways as well as the biological relationship to these tumours.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ACKNOWLEDGMENTS

We thank Dr. ir. B.M.R. Kramer from the university library of the University Utrecht (UU) for her help with the literature search.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2020.102970.

References

Agarwal, K., 2017. An Unusual Presentation of Metanephric Adenofibroma: A Rare Case Report. J. Clin. DIAGNOSTIC Res. https://doi.org/10.7860/JCDR/2017/30881.10699.

Argani, P., 2005. Metanephric neoplasms: the hyperdifferentiated, benign end of the Wilms tumor spectrum? Clin. Lab. Med. 25, 379–392. https://doi.org/10.1016/j.cll.2005.01.002.

Argani, P., Beckwith, J.B., 2000. Metanephric stromal tumor: report of 31 cases of a distinctive pediatric renal neoplasm. Am. J. Surg. Pathol. 24, 917–926.

Argani, P., Lee, J., Netto, G.J., Zheng, G., Tseh-Lin, M., Park, B.H., 2016. Frequent BRAF V600E Mutations in Metanephric Stromal Tumor. Am. J. Surg. Pathol. 40, 719–722. https://doi.org/10.1097/PAS.0000000000000603.

Arroyo, M.R., Green, D.M., Perlman, E.J., Beckwith, J.B., Argani, P., 2001. The spectrum of metanephric adenofibroma and related lesions: clinicopathologic study of 25 cases from the National Wilms Tumor Study Group Pathology Center. Am. J. Surg. Pathol. 25, 433–444.

Barroca, H.M.M.T., Cirnes, L., Lopes, J.M., 2016a. Metanephric adenoma: Cytological, histological, and molecular diagnosis of a case. Diagn. Cytopathol. 44, 263–266. https://doi.org/10.1002/dc.23427.

Barroca, H.M.M.T., Cirnes, L., Lopes, J.M., 2016b. Metanephric adenoma: Cytological, histological, and molecular diagnosis of a case. Diagn. Cytopathol. 44, 263–266. https://doi.org/10.1002/dc.23427.

Bastos Netto, J.M., Esteves, T.C., Mattos, R.de C.M.S, Tibiriçá, S.H.C., Costa, S.M.C.R., Vieira, L.J., 2007. Metanephric adenoma: a rare differential diagnosis of renal tumor in children. J. Pediatr. Urol. 3, 340–341. https://doi.org/10.1016/j.jpurol.2006.10.003.

Beckwith, J., 1998. Metanephric stromal tumor (MST): a new renal neoplasm resembling mesoblastic nephroma (MN) but related to metanephric adenofibroma (MAF). Mod Pathol 11, 1.

Benson, M., Lee, S., Bhattacharya, R., Vasy, V., Zuberi, J., Yasmeen, S., Ahmed, M., Hanna, M.K., 2018. Metanephric Adenoma in the Pediatric Population: Diagnostic Challenges and Follow-up. Urology 120, 211–215. https://doi.org/10.1016/j.urology.2018.06.042.

Brisigotti, M., Cozzutto, C., Fabbretti, G., Sergi, C., Callea, F., 1992. Metanephric adenoma. Histol. Histopathol. 7, 689–692.

Burger, M., Junker, K., Denzinger, S., Schubert, T., Stoehr, R., Wieland, W.-F., Hartmann, A., 2007. Metanephric adenoma of the kidney: a clinicopathological and molecular study of two cases. J. Clin. Pathol. 60, 832–833. https://doi.org/10.1136/jcp.2005.036103.

Chami, R., Yin, M., Marrano, P., Teerapakpinyo, C., Shuangshoti, S., Thorner, P.S., 2015. BRAF mutations in pediatric metanephric tumors. Hum. Pathol. 46, 1153–1161. https://doi.org/10.1016/j.humpath.2015.03.019.

Choueiri, T.K., Cheville, J., Palescandolo, E., Fay, A.P., Kantoff, P.W., Atkins, M.B., McKenney, J.K., Brown, V., Lampron, M.E., Zhou, M., Hirsch, M.S., Signoretti, S., 2012. BRAF mutations in metanephric adenoma of the kidney. Eur. Urol. 62, 917–922. https://doi.org/10.1016/j.eururo.2012.05.051.

Comerci, S.C., Levin, T.L., Ruzal-Shapiro, C., Berdon, W.E., Beckwith, J.B., Hibshoosh, H., Hurlet-Jensen, A., Sitarz, A.L., 1996. Benign adenomatous kidney neoplasms in children with polycythemia: imaging findings. Radiology 198, 265–268. https://doi.org/10.1148/radiology.198.1.8539391.

Davis, C.J., Barton, J.H., Sesterhenn, I.A., Mostofi, F.K., 1995. Metanephric adenoma. Clinicopathological study of fifty patients. Am. J. Surg. Pathol. 19, 1101–1114.

De Pasquale, M.D., Diomedi-Camassei, F., Serra, A., Boldrini, R., Inserra, A., Caione, P., Jenkner, A., 2011. Recurrent metanephric stromal tumor in an infant. Urology 78, 1411–1413. https://doi.org/10.1016/j.urology.2011.04.029.

Drut, R., Drut, R.M., Ortolani, C., 2001. Metastatic metanephric adenoma with foci of papillary carcinoma in a child: a combined histologic, immunohistochemical, and FISH study. Int. J. Surg. Pathol. 9, 241–247. https://doi.org/10.1177/106689690100900313.

Galluzzo, M.L., Garcia de Davila, M.T., Vujanić, G.M., 2012. A composite renal tumor: metanephric adenofibroma, Wilms tumor, and renal cell carcinoma: a missing link? Pediatr. Dev. Pathol. 15, 65–70. https://doi.org/10.2350/11-03-1007-CR.1.

Guzman, E., Turc-Carel, C., Soler, C., Pierre, C., Chevallier, P., Michiels, J.F., 2000. Nephrogenic adenofibroma in a young child. Pathol. Res. Pract. 196, 853–856. https://doi.org/10.1016/S0344-0338(00)80088-6.

Hennigar, R.A., Beckwith, J.B., 1992. Nephrogenic adenofibroma. A novel kidney tumor of young people. Am. J. Surg. Pathol. 16, 325–334.

Kacar, A., Azili, M.N., Cihan, B.S., Demir, H.A., Tiryaki, H.T., Argani, P., 2011. Metanephric stromal tumor: a challenging diagnostic entity in children. J. Pediatr. Surg. 46, e7–e10. https://doi.org/10.1016/j.jpedsurg.2011.08.023.

Kato, H., Suzuki, M., Aizawa, S., Hano, H., 2003. Metanephric adenoma of the kidney with massive hemorrhage and necrosis: immunohistochemical, ultrastructural, and flow cytometric studies. Int. J. Surg. Pathol. 11, 345–352. https://doi.org/10.1177/106689690301100418.

Kinney, S.N., Eble, J.N., Hes, O., Williamson, S.R., Grignon, D.J., Wang, M., Zhang, S., Baldrige, L.A., Martignoni, G., Brunelli, M., Wang, L., Comperat, E., Fan, R., Montironi, R., MacLennan, G.T., Cheng, L., 2015. Metanephric adenoma: the utility of immunohistochemical and cytogenetic analyses in differential diagnosis, including solid variant papillary renal cell carcinoma and epithelial-predominant nephroblastoma. Mod. Pathol. 28, 1236–1248. https://doi.org/10.1038/modpathol.2015.81.

Kohashi, K., Oda, Y., Nakamori, M., Yamamoto, H., Tamiya, S., Toubo, T., Kinoshita, Y., Tajiri, T., Taguchi, T., Tsuneyoshi, M., 2009. Multifocal metanephric adenoma in childhood. Pathol. Int. 59, 49–52. https://doi.org/10.1111/j.1440-1827.2008.02324.x.

Konety, B.R., Hord, J.D., Weiner, E.S., Schneck, F.X., 1998. Embryonal adenoma of the kidney associated with polycythemia and von Willebrand disease. J. Urol. 160, 2171–2174.

Küpeli, S., Baydar, D.E., Canakl, F., Yalçn, B., Kösemehmetoğlu, K., Tekgül, S., Büyükpamukçu, M., 2009b. Metanephric adenoma in a 6-year-old child with hemihypertrophy. J. Pediatr. Hematol. Oncol. 31, 453–455. https://doi.org/10.1097/MPH.0b013e31819e8f72.

Mangray, S., Breese, V., Jackson, C.L., Lombardo, K., Taliano, R., Resnick, M., Yakirevich, E., 2015. Application of BRAF V600E mutation analysis for the diagnosis of metanephric adenofibroma. Am. J. Surg. Pathol. 39, 1301–1304. https://doi.org/10.1097/PAS.0000000000000501.

Marsden, L., Jennings, L.J., Gadd, S., Yu, M., Perlman, E.J., Cajaiba, M.M., 2017. BRAF exon 15 mutations in pediatric renal stromal tumors: prevalence in metanephric stromal tumors. Hum. Pathol. 60, 32–36. https://doi.org/10.1016/j.humpath.2016.09.025.

McNeil, J.C., Corbett, S.T., Kuruvilla, S., Jones, E.A., 2008. Metanephric adenoma in a five-year-old boy presenting with chyluria: case report and review of literature. Urology 72, 545–547. https://doi.org/10.1016/j.urology.2008.04.010.

Moch, H., Cubilla, A.L., Humphrey, P.A., Reuter, V.E., Ulbright, T.M., Catto, J., 2016. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. Eur. Assoc. Urol 120–123. https://doi.org/10.1016/j.eururo.2016.02.029.

Pagès, A., Granier, M., 1980. Le néphrome néphronogène. Arch Anat Cytol Pathol 28, 99–103.

Palese, M.A., Ferrer, F., Perlman, E., Gearhart, J.P., 2001. Metanephric stromal tumor: a rare benign pediatric renal mass. Urology 58, 462.

Pasricha, S., Gandhi, J.S., Gupta, G., Mehta, A., Beg, S., 2012. Bilateral, multicenteric metanephric adenoma associated with Wilms' tumor in a child: a rare presentation with important diagnostic and therapeutic implications. Int. J. Urol. 19, 1114–1117. https://doi.org/10.1111/j.1442-2042.2012.03134.x.

Polosukhina, D., Love, H.D., Correa, H., Su, Z., Dahlman, K.B., Pao, W., Moses, H.L., Arteaga, C.L., Lovvorn, H.N., Zent, R., Clark, P.E., Clark, P.E., 2017. Functional KRAS mutations and a potential role for PI3K/AKT activation in Wilms tumors. Mol. Oncol. 11, 405–421. https://doi.org/10.1002/1878-0261.12044.

Pritchard-Jones, K., Bergeron, C., de Camargo, B., van den Heuvel-Eibrink, M.M., Acha, T., Godzinski, J., Oldenburger, F., Boccon-Gibod, L., Leuschner, I., Vujanic, G., Sandstedt, B., de Kraker, J., van Tinteren, H., Graf, N., SIOP Renal Tumours Study Group, 2015. Omission of doxorubicin from the treatment of stage II-III, intermediate-risk Wilms' tumour (SIOP WT 2001): an open-label, non-inferiority, randomised controlled trial. Lancet (London, England) 386, 1156–1164. https://doi.org/10.1016/S0140-6736(14)62395-3.

Raj, P., Khanolkar, A., Sarin, Y.K., 2016. Metanephric Adenofibroma Masquerading as Wilms' Tumor. APSP J. Case Rep. 7, 37. https://doi.org/10.21699/ajcr.v7i5.463.

Rakheja, D., Lian, F., Tomlinson, G.E., Ewalt, D.H., Schultz, R.A., Margraf, L.R., 2005. Renal metanephric adenoma with previously unreported cytogenetic abnormalities: case report and review of the literature. Pediatr. Dev. Pathol. 8, 218–223. https://doi.org/10.1007/s10024-004-7081-3.

Renshaw, A.A., Freyer, D.R., Hammers, Y.A., 2000. Metastatic metanephric adenoma in a child. Am. J. Surg. Pathol. 24, 570–574.

Saltzman, A.F., Carrasco, A., Maccini, M.A., Caldwell, B.T., Treece, A.L., Cost, N.G., 2017. Large Cystic Metanephric Adenoma in a 15-Year-Old Girl. Urology 101, 147–150. https://doi.org/10.1016/j.urology.2016.12.019.

Scharfenberg, J., Beckman, E., 1984. Persistent renal blastemal in an adult. Hum. Pathol. 15, 791–793.

Shek, T.W., Luk, I.S., Peh, W.C., Chan, K.L., Chan, G.C., 1999. Metanephric adenofibroma: report of a case and review of the literature. Am. J. Surg. Pathol. 23, 727–733.

Wegert, J., Vokuhl, C., Collord, G., Del, M., Velasco-Herrera, C., Farndon, S.J., Guzzo, C., Jorgensen, M., Anderson, J., Slater, O., Duncan, C., Bausenwein, S., Streitenberger, H., Ziegler, B., Furtwängler, R., Graf, N., Stratton, M.R., Campbell, P.J., Jones, D.T., 2018. Recurrent intragenic rearrangements of EGFR and BRAF in soft tissue tumors of infants. Nat. Comm. 9, 4. https://doi.org/10.1038/s41467-018-04650-6.

Werbrouck, P., Casselman, J., Defloor, E., 1990. Embryonal adenoma of the kidney. Eur. Urol. 17, 264–266.

Wobker, S.E., Matoso, A., Pratilas, C.A., Mangray, S., Zheng, G., Lin, M.-T., Debeljak, M., Epstein, J.I., Argani, P., 2019. Metanephric Adenoma-Epithelial Wilms Tumor Overlap Lesions: An Analysis of BRAF Status. Am. J. Surg. Pathol. https://doi.org/10.1097/PAS.0000000000001240.

Yin, M., Cai, J., Thorner, P.S., 2015. Congenital renal tumor: metanephric adenoma, nephrogenic rest, or malignancy? Pediatr. Dev. Pathol. 18, 245–250. https://doi.org/10.2350/15-01-1595-CR.1.

Yoshioka, K., Miyakawa, A., Ohno, Y., Namiki, K., Horiguchi, Y., Murai, M., Mukai, M., Tachibana, M., 2007. Production of erythropoietin and multiple cytokines by metanephric adenoma results in erythrocytosis. Pathol. Int. 57, 529–536. https://doi.org/10.1111/j.1440-1827.2007.02136.x.

Zhang, L.J., Yang, G.F., Shen, W., Lu, G.M., 2011. CT and ultrasound findings of metanephric adenoma: a report of two cases and literature review. Br. J. Radiol. 84, e51–e54. https://doi.org/10.1259/bjr/62994226.