CASE REPORT

Functioning metastatic paraganglioma of the urinary bladder in a 10-year-old child

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SUMMARY

Paragangliomas of the urinary bladder are very rare tumours representing less than 1% of bladder tumours. Preoperative diagnosis is essential to avoid perioperative complications related to catecholamine release. A high index of suspicion should be maintained when the classical symptoms of voiding-related paroxysms of headache, palpitation and dizziness are present. We present a rare case of malignant paraganglioma of the urinary bladder in a 10-year-old boy. The patient had the classic presentation. We review the radiological diagnostic tools and findings of this rare entity.

BACKGROUND

Pheochromocytomas are tumours of chromaffin cells that arise from the adrenal gland. They can, however, arise in 10%–20% of the cases from sympathetic tissue outside the adrenals and are then called paragangliomas.^{1,2} Paragangliomas of the urinary bladder are very rare, representing 0.06% of bladder tumours.³ These are typically functional and commonly present with symptoms of paroxysmal hypertension, palpitations and micturition syncope while a proportion of cases present with non-specific symptoms of a bladder tumour such as painless haematuria, abdominal fullness and pain.^{4,5}

Malignant paragangliomas are those that demonstrate invasive potential or distant metastasis.² They are more common in patients with certain predisposing syndromes, such as succinate dehydrogenase B mutations.²

CASE PRESENTATION

A 10-year-old boy presented to his primary care physician with a 4-month history of a weak urinary stream, occasional headache, sweating and dizziness when straining for defecation or urination. Physical examination and vital signs on presentation were unremarkable, in particular, the heart rate and blood pressure were within normal limits. Urinalysis on presentation was negative for haematuria but showed trace protein.

INVESTIGATIONS

Ultrasound of the pelvis was done and showed a 3 cm echogenic bladder mass. Further characterisation by MRI of the pelvis showed a 2.5×2.7×2.4 cm (anteroposterior (AP), craniocaudal and transverse diameters, respectively) lobulated mass centred at left posterior wall/bladder base protruding into the bladder lumen showing slight heterogeneous salt

and pepper appearance that is hyperintense on T2 and slightly hypointense on T1-weighted imaging (WI) (figure 1A–C). Following contrast administration, the mass showed significant enhancement with a non-enhancing centre suggestive of necrosis (figure 1D,E). On diffusion-weighted imaging (DWI), mild restriction was seen at its peripheral aspect (figure 1F,G).

A cystoscopic biopsy was considered but there was concern regarding the origin of the tumour: it was not clear whether it was a bladder mass or a pelvic mass abutting the bladder. The patient's urethral size was also of concern, for the paediatric resectoscope may yield an inconclusive sample. These circumstances led the surgeon to conclude that a cystoscopic biopsy may prove to be of low yield. He, therefore, underwent a CT-guided biopsy of the mass with no complications. Immunohistochemistry of the tumour cells was positive for synaptophysin, chromogranin, CD56 and INI-1. It was negative for myogenin, desmin, CKAE1/3, CD99, WT-1, S-100 and melan-A. Ki-67 was low. The favoured diagnosis was paraganglioma.

Plasma and urine samples were, then, collected to measure metanephrine, normetanephrine, catecholamines (Bioscientia GmbH-Ingelheim, Germany) and vanillylmandelic acid levels (Cerba Laboratory France). Plasma and urine normetanephrines, norepinephrine and urine dopamine were elevated (table 1).

Ten days later, nuclear medicine imaging for staging of the tumour was done. The patient received 3.9 mCi of ¹²³I-MIBG, images of the body using single-photon emission CT (SPECT)/CT were obtained 4 and 24 hours later showing physiological distribution of the radiotracer. The primary bladder mass was photopenic on SPECT/CT (figure 2).

One week later, positron emission tomography (PET)-CT of the whole body was performed following intravenous injection of 3.43 mCi of Gallium DOTA-TOC with 45 min uptake time after which imaging was started. Radiotracer avid left bladder mass and metastatic lymph node in the left external iliac chain was seen (figure 3).

TREATMENT

The patient was then scheduled to undergo partial cystectomy with iliac lymphadenectomy. Through a midline infraumbilical incision, a 2.2×1.5×1 cm tan-yellow well-circumscribed exophytic mass with a fibrotic centre and nodular borders was excised (figure 4). The left ureter had to be divided for

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Figure 1 MRI of the pelvis: Coronal (A) and axial (B) T2WI with fat suppression demonstrate a heterogeneous salt and pepper appearance of a hyperintense mass (white arrows) arising from the left bladder base. (C) T1WI image shows the mass to be intermediate to slightly hypointense (white arrow). (D) T1WI postintravenous contrast administration shows significant enhancement (white arrow). (E) The intensity of enhancement is better appreciated on fat suppressed SPIR T1WI postcontrast where a tiny central hypoenhancement is noted likely related to necrosis (white arrow). (F) AxialDWI: the mass is showing restricted diffusion with a high signal on diffusion images (white arrow) and (G) low signal on the ADC map (black arrow). ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; SPIR, spectral presaturation with inversion recovery. T1WI, T1-weighted imaging; T2WI, T2-weighted imaging.

complete resection of the tumour and it was reimplanted at the posterior bladder wall. In addition, four left iliac lymph nodes were also excised and sent to pathology. On immunohistochemistry, tumour cells were positive for chromogranin, CD56 and synaptophysin. S-100 highlights the presence of sustentacular cells confirming the diagnosis of paraganglioma. One of the four lymph nodes showed metastatic paraganglioma confirming the findings on PET scan.

OUTCOME AND FOLLOW-UP

On the postoperative day 10, plasma catecholamines and metanephrines were back to normal (table 2). Six months after the surgical resection, the patient is still asymptomatic. The patient is being followed up with regular catecholamine levels and MRI of the abdomen and pelvis with no sign of recurrence.

DISCUSSION

Bladder tumours are rare in the paediatric population, with rhabdomyosarcoma being the most common constituting 32% of bladder tumours.⁶ The classical presentation of bladder tumour is painless haematuria. Some patients can present with

obstructive symptoms such as urgency, frequency and dysuria. Paragangliomas of the urinary bladder, in particular, are very uncommon, representing about 1% of paediatric bladder tumours.^{6 7} In 2013, a systematic review of urinary bladder pheochromocytomas showed a wide range of presenting symptoms ranging from catecholamine-related symptoms such as headaches, hypertension and palpitations to local symptoms of haematuria, dysuria and abdominal pain.⁴ The most common presenting symptoms were micturition associated attacks of catecholamine release like in our patient.⁵

The initial workup of a patient presenting with urinary symptoms is a urinalysis with microscopic evaluation of the urine.

Figure 2 Following the intravenous injection of ¹²³I-MIBG, images of the body showed normal distribution of radiotracer with no focal areas of abnormal increased uptake. MIBG, metaiodobenzylguanidine.

Table 1 Preoperative plasma and urine metanephrine, normetanephrine, catecholamine and vanillylmandelic acid levels

	Test	Results	Reference range
Plasma	Free metanephrine	<50.0 ng/L	<90.0 ng/L
	Free normetanephrine	1320.0 ng/L	<129 ng/L
	Epinephrine	<20 ng/L	up to 84 ng/L
	Norepinephrine	1860 ng/L	420 ng/L
Urine	Dopamine	<20 ng/L	85 ng/L
	Vanillylmandelic acid	8.6 mg/g	<11.30 mg/g
	Epinephrine	<3 µg/24 hours	<27
	Norepinephrine/creatinine	802 µg/g	<80.0
	Dopamine/creatinine	632 µg/g	<540
	Metanephrine/creatinine	128 µg/g	40–220
	Normetanephrine/creatinine	4079 µg/24 hours	81–583

Figure 3 Gallium DOTA-TOC PET/CT: (A) coronal MIP image shows the lymph node in the left external iliac chain (black arrow) and the mass arising from the left wall of the urinary bladder (arrow head). (B) Axial MIP image shows the mass arising from the posterior wall of the bladder (white arrows). (C) Axial MIP image shows the left external iliac chain lymph node. (D and E) Axial PET-CT images show the Gallium 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-(Tyr³)-octreotide (DOTA-TOC) avid mass (white arrows) arising from the left posterior bladder wall. (F) Axial PET-CT image shows the gallium DOTA-TOC avid left external iliac lymph node (white arrow), consistent with nodal metastasis. MIP, maximum intensity projection; PET-CT, positron emission tomography—CT.

The urinalysis can give a clue for the origin of the symptoms and can help differentiate upper from lower urinary tract aetiologies.

If there is suspicion for a bladder mass, then cystoscopy is the gold standard for further evaluation. The procedure can be done in the office with minimal risks, and can allow for direct visualisation of the lesion and biopsies of the lesion can be taken.

Radiological imaging may be needed to evaluate the size, location and spread of the mass. Ultrasonography is a quick initial tool to confirm the presence, location and size of the tumour.⁸ The sonographic appearance is usually non-specific irregular mass with low to intermediate echotexture.⁸ Cystoscopy and tissue biopsy for pathology are still required to make the diagnosis of bladder malignancy.

CT scan and MRI can be done before or after the biopsy for staging of the tumour. They can provide essential information on the local spread of the tumour, nodal metastasis and distant metastasis, with MRI being superior to CT due to better delineation of soft tissues.^{9–11}

In our case, an ultrasound was done for the evaluation of urinary symptoms confirming the presence of a bladder mass that was further characterised by MRI. None of these modalities could however confirm the diagnosis of paraganglioma although clinically suspected and a CT-guided biopsy was necessary to establish this unusual diagnosis.

Paragangliomas typically occur in the third to fifth decades of life with a wide range of distribution. In our case, we present a 10-year-old boy with a metastatic bladder paraganglioma which is the youngest in the English literature.

Figure 4 Gross pathology of the excised mass (top) and the positive lymph node (bottom).

These rare tumours present a diagnostic challenge due to their rarity as compared with more common benign and malignant tumours of the bladder. A suspicion of paraganglioma is raised by the existence of symptoms related to catecholamine release especially symptoms that are temporally related to micturition. As structural imaging is not typically helpful in the diagnosis of paraganglioma of the urinary bladder, in the upcoming section, we will focus on the diagnostic performance of nuclear medicine imaging tools.

Nuclear imaging diagnosis

When bladder paragangliomas are functional and symptomatic, and laboratory test are confirmatory, pretherapy nuclear imaging can be done using nuclear isotope tracers. The staging of the tumours is crucial to guide the treatment of extra-adrenal paragangliomas.¹² ¹³¹I/¹²³I-Metaiodobenzylguanidine (MIBG) scintigraphy and ¹¹¹In-diethylenetriaminepentaacetic acid (DTPA)-pentetreotide scintigraphy are the most commonly used conventional nuclear imaging techniques for pheochromocytoma and paragangliomas. MIBG is taken

Table 2 Plasma catecholamines and metanephrines on postoperative day 10

	Test	Results	Reference range
Plasma	Free metanephrine	<50.0 ng/L	<90.0 ng/L
	Free normetanephrine	92 ng/L	<129 ng/L
	Epinephrine	43 ng/L	up to 84 ng/L
	Norepinephrine	278 ng/L	420 ng/L
	Dopamine	<20 ng/L	85 ng/L

Table 3 Genetic syndromes associated with paraganglioma and pheochromocytoma

Syndrome	Gene	Associated tumours	Malignancy rate
MEN 2	RET protooncogene	A: Medullary thyroid carcinoma Pheochromocytoma Hyperparathyroidism Cutaneous lichen amyloidosis B: Medullary thyroid carcinoma Pheochromocytoma Multiple neuromas Marfanoid habitus	3%
Von Hippel-Lindau	VHL	Type 2 (with pheochromocytoma) A: Retinal and CNS haemangioblastomas Pheochromocytomas endolymphatic sac tumours Epididymal cystadenomas B: Renal cell cysts and carcinomas Retinal and CNS pheomangioblastomas Pancreatic neoplasms and cysts Pheochromocytomas Endolymphatic sac tumours Epididymal cystadenomas C: Pheochromocytomas only	5%
PGL1	SDHD	Pheochromocytomas	<3%
PGL2	SDHAF2		
PGL3	SDHC		
PGL4	SDHB		50%
PGL5	SDHA		
Neurofibromatosis	NF1	Multiple fibromas on skin and mucosa 'Café au lait' skin spots Pheochromocytomas	

CNS, central nervous system; MEN 2, multiple endocrine neoplasia type 2; PGL1–5, paraganglioma syndrome type 1 to 5.

up by chromaffin tissue via the norepinephrine transporter and DTPA-pentetreotide binds to somatostatin receptor 2.¹² However, dedifferentiated cells especially in metastatic tumours tend to lack the markers necessary for these tracers and thus decreasing the sensitivity of SPECT imaging with MIBG and DTPA-pentetreotide.

PET scanning offers a higher spatial resolution and therefore has an even higher accuracy than MIBG SPECT.¹³ Radiotracers used with PET scanning for the localisation of pheochromocytomas and paragangliomas include 18F-FDOPA which was found to be more sensitive than MIBG scintigraphy in the staging and restaging of paragangliomas.¹⁴ Additionally, 68Ga DOTATOC and 68Ga-DOTATATE PET/CT were found to be superior to 123I-MIBG SPECT in some cases of aggressive paraganglioma, probably associated with a certain level of functional dedifferentiation.¹⁵ Henri *et al*,¹⁶ in a prospective study of 216 patients with suspected paraganglioma and pheochromocytoma, compared MIBG SPECT with fluorodeoxyglucose (FDG)-PET and found that PET had a higher sensitivity (82.5%) than MIBG (50%) in detecting metastasis. Finally, in a study of 30 patients with succinate dehydrogenase subunit B (SDHB)-associated pheochromocytoma and paraganglioma, FDG PET has a sensitivity approaching 100% in the detection of metastasis while MIBG had 80% sensitivity.¹⁷

In our case, the metastatic lymph node was not detected with MIBG SPECT but was easily visible on PET scan with Gallium DOTA-TOC. This is possibly due to the size of the lymph node or the dedifferentiation of chromaffin cells leading to loss of the necessary receptors for MIBG.

Genetics

Although they can occur sporadically, pheochromocytomas and paragangliomas have been associated with many genetic disorders, notably, multiple endocrine neoplasia (MEN) 2a and 2b, Von Hippel-Lindau, familial paraganglioma syndromes which are divided into five subtypes depending on the

succinate dehydrogenase subunit mutation involved.^{18 19} Table 3 summarises the genetic syndromes with the associated mutations.²⁰

In urinary bladder paragangliomas, a mutation in the SDHB is the most common which is the mutation associated with the highest rate of metastasis.¹⁶

Learning points

- ▶ The classic presentation of micturition-related headache, palpitation and dizziness is the most common and should raise suspicion for paraganglioma in the urinary bladder.
- ▶ Findings by ultrasound, CT scan and MRI are non-specific and are not diagnostic.
- ▶ Metaiodobenzylguanidine (MIBG) single-photon emission-CT is specific to this type of tumours and can be used prior to biopsy if there is suspicion of PGL.
- ▶ For staging and metastatic workup fluorodeoxyglucose, Ga-DOTATOC, Ga-DOTATATE, or F-DOPA positron emission tomography scan are more sensitive than MIBG scan due to a dedifferentiation of metastatic lesions.

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