Contrast-enhanced ultrasound (CEUS) appearances of an adrenal phaeochromocytoma in a child with Von Hippel-Lindau disease

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Abstract A phaeochromocytoma is a rare catecholamine-secreting tumour arising from the chromaffin cells. We describe a case of a child with Von Hippel-Lindau disease, with an adrenal phaeochromocytoma who presented with severe dilated cardiomyopathy driven by secondary hypertension. Contrast-enhanced ultrasound findings are described and compared with both magnetic resonance imaging and computed tomography imaging.

Keywords Ultrasound · Contrast-enhanced ultrasound (CEUS) · Adrenal gland · Phaeochromocytoma · Paediatrics

Sommario Il feocromocitoma è un tumore secernente catecolamine, raro; deriva dalle cellule cromaffini. Descriviamo il caso di un bambino con malattia di Von Hippel-Lindau, con feocromocitoma surrenale che si è presentato con grave cardiomiopatia dilatativa causata da ipertensione secondaria. Vengono descritte le caratteristiche ecografiche

con mezzo di contrasto, comparate sia a risonanza magnetica che a tomografia computerizzata.

Introduction

A 11-year-old child presented with severe dyspnoea and was found to have dilated hypertrophic hypertensive cardiomyopathy and heart failure. At physical examination, the patient was hypertensive (blood pressure 160/110). Notable laboratory findings included urinary noradrenaline (2,068 nmol/mmol creatinine; reference range <50 nmol/mmol creatinine) and plasma and urinary normetadrenaline (plasma 28.14 nmol/L; reference range <2.19 nmol/L and urinary 8.08 µmol/mmol creatinine; reference range <0.28 µmol/mmol creatinine) levels that were all greater than normal. Normal urinary adrenaline and urinary and plasma meta-adrenaline levels were recorded. The patient's family history was unremarkable and the patient's own medical history included significant asthma and hay fever. During the admission the patient suffered a left middle cerebral artery cerebrovascular stroke secondary to a left ventricular thrombus. Ultrasound (US) and magnetic resonance (MR) imaging were performed for abdominal evaluations. MR imaging revealed a well-defined left suprarenal mass measuring $5.2 \times 4.1 \times 3.5$ cm, heterogeneous in signal intensity but predominantly high signal on T2-weighted sequences and intermediate signal on T1 weighted sequences. Following gadolinium contrast-enhanced MR imaging, a thick, irregular rim of enhancing tissue with a central area of non-enhancement compatible with tumour necrosis was seen (Fig. 1a, b). The exact interpretation was uncertain with the differential diagnosis including phaeochromocytoma, tumours of the neuroblastoma spectrum, adrenocortical

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Fig. 1 **a** Axial T2 weighted image at the level of the kidneys and spleen, demonstrating a mass arising from the left adrenal (*arrow*) of high signal intensity. **b** Axial T1 weighted fat saturation post-contrast administration, imaged in the venous phase, enhancement of the thickened peripheral aspect of the lesion (*arrow*) is noted, with central lesion necrosis

Fig. 2 Axial image contrast-enhanced venous phase CT image at the level of the left-sided adrenal lesion, demonstrates peripheral rim enhancement and central necrosis (*arrow*)

carcinoma or adenoma. Given the clinical presentation in keeping with a functioning tumour, pheochromocytoma was considered the most likely diagnosis. The patient underwent further imaging, which included a computed tomography (CT) examination (Fig. 2), a radionuclide metaiodobenzylguanidine (mIBG) study and a contrast-enhanced ultrasound (CEUS). The CEUS study was conducted using SonoVueTM (Bracco SpA, Milan) as contrast with a dose of 1.2 mL, on a Siemens S2000 (Siemens AG, Mountain View, CA, USA) deploying a 4 MHz curvilinear transducer, and using a low mechanical index (MI) program (CPSTM, Siemens AG). On the B-mode examination, the well-circumscribed abnormality was isoechoic to the adjacent liver with a central hypoechoic area seen, with colour Doppler non-informative (Fig. 3a). The CEUS examination demonstrated rapid and equal enhancement to the liver in the arterial phase with no enhancement in the central aspect of the lesion (Fig. 3b). The lesion remained iso-enhancing to the liver in the early venous phase (Fig. 3c) and until the later venous phase where washout was seen (Fig. 3d). Further genetic evaluation was pursued and the child was found to be

a 25 % mosaic for Von Hippel-Lindau (VHL) missense mutation in exon 3.

The patient underwent primary open surgery by a rooftop incision, as imaging had shown possible invasion of the left renal vein. Exploration of the left retroperitoneum found a 6 cm highly vascular mass with direct arterial contributories from renal artery, splenic artery and aorta. The adrenal vein drained into the left renal vein but had been consumed by the tumour so that the mass was removed creating a small opening in the wall of the renal vein. This was repaired by direct stitches. There was no associated lymphadenopathy and no other established sign of malignancy.

Macroscopically, the mass measured $6.5 \times 4.5 \times 3.0$ cm and weighed 50 g. It had a smooth external surface. The cut surface was yellow in colour with a haemorrhagic centre (Fig. 4a). On histology, sections of the adrenal mass showed a tumour surrounded by a pseudo-capsule, which separated it from a thin rim of normal adrenal gland. The tumour had a mixture of trabecular and nested architecture, with large tumour cells, with granular pink cytoplasm and central nuclei with prominent nucleoli. Mild nuclear pleomorphism was present and occasional mitotic figures were seen; features of a pheochromocytoma (Fig. 4b).

Discussion

A pheochromocytoma is a rare primary neoplasm of the adrenal medulla that may produce catecholamines, occurring mainly in adults, usually benign, with malignancy accounting for 10 %. Extra-adrenal pheochromocytomas arise from paraganglionic chromaffin tissue of the sympathetic nervous system, and may occur anywhere from the base of the brain to the urinary bladder. Extra-adrenal pheochromocytomas are termed paragangliomas [1]. A classic triad of symptoms that includes headache, sweating, and palpitations has been described in functional tumours. A pheochromocytoma and functional paraganglioma may present with acute catecholamine cardiomyopathy (in

Fig. 3 **a** Sagittal grey-scale image through the spleen demonstrating the left adrenal lesion, with a central area of low echogenicity (*arrow*). **b** Arterial phase, 14 s following microbubble contrast administration, in the arterial phase there is rim enhancement of the adrenal lesion, with absence of enhancement in the central aspect of the lesion (*arrow*). **c** Early venous phase, at 41 s following microbubble contrast administration, there is some washout of the peripheral aspect of the lesion, and continuing non-enhancement of the central aspect (*arrow*). **d** Late venous phase, at 85 s following microbubble contrast administration, there is continuing washout of the peripheral aspect of the lesion, and continuing non-enhancement of the central aspect (*arrow*)

Fig. 4 **a** Macro-specimen of the left adrenal gland showing a well-circumscribed mass with a yellow cut surface and haemorrhagic centre. **b** Sections through the lesion demonstrate features of a

phaeochromocytoma: nested/trabecular architecture with large tumour cells containing pink cytoplasm and central nuclei (haematoxylin and eosin stain, $\times 10$ magnification)

11 %), suggesting that these tumours should be suspected in patients with acute heart failure without evidence of valvular or coronary artery disease [2]. As many as 10 % of phaeochromocytomas were thought to be familial, but as recently described, 25 % of apparently sporadic phaeochromocytomas are essentially due to an occult germ-line mutation in either Von Hippel-Lindau (VHL), proto oncogene RET (REarranged during Transfection), or one

of succinate dehydrogenase genes (SHBD, SHDD) [3]. When a phaeochromocytoma is linked to these genetic syndromes, there is a significantly higher prevalence of bilateral tumours. A phaeochromocytoma is a rare entity in children, and warrants a genetic analysis; the underlying VHL missense mutation was found in this case. VHL disease displays complex genotype-phenotype correlations and can be classified according to the absence (type 1) or

presence (type 2) of pheochromocytoma. This syndrome is also characterized by the additional presence of central nervous system and retinal haemangioblastomas as well as clear-cell renal carcinomas [4].

Pheochromocytomas may have almost any pathological and imaging appearance and may present as a solid or partially cystic lesion with region of heterogeneity and necrotic changes [5, 6]. Ultrasound of the abdomen is the appropriate first imaging method and lesions suspicious for pheochromocytoma are usually sharply demarcated with a largely homogeneous echo texture with cystic components [7, 8]. Traditionally, CT imaging evaluation with MR imaging as an adjuvant is used to characterise adrenal lesions, with no role for ultrasound outside detection. Although these lesions can show differential pattern of enhancement following contrast-enhanced CT imaging, reflecting the variable pathological presentation, pheochromocytomas typically enhance avidly in the arterial phase and on delayed contrast-enhanced CT examinations, are reported to have contrast enhancement loss that is similar to that of adrenal metastases and significantly less than that of adrenal adenomas [9]. On MR imaging, most pheochromocytomas demonstrate low signal intensity on T1 weighted images and high signal intensity on T2-weighted images, the so-called light bulb sign and appearing still more hyperintense on fat-suppressed T2 weighted images due to rescaling effect of signal intensity. After administration of gadolinium-based contrast, pheochromocytoma enhances avidly on T1 weighted images [10].

Ultrasound microbubble contrast agents have been recently introduced into clinical practice, and are widely used in the adult population in a variety of organs [11, 12], and more recently have gained recognition in the paediatric population [13]. Whereas the contrast agents used in CT and MR imaging are cleared from the blood to the interstitial spaces, microbubbles are confined to the intravascular space, making this an ideal agent for the demonstration of vascularity of a lesion [14]. Furthermore with children, the ability to ensure a diagnostic study with ultrasound combined with microbubbles is achievable without the difficulties associated with CT and MR imaging with contrast agents [15]. The microbubble contrast is not licensed for use in the paediatric population but this should not deter the physician from using the agents; most drugs in regular use in the paediatric population are not registered [16] and regulatory bodies allow for physician-led off-licence use [17, 18].

Despite the advantages of a CEUS examination in a paediatric patient, knowledge about evaluation of adrenal abnormalities on CEUS is limited and controversial even in the adult population. Sensitivity of 50–100 % in distinguishing malignant and benign lesions on the basis of the enhancing pattern alone is reported [19]. Adrenal lesions

have been described as hypovascular, isovascular and hypervascular on the basis of comparison with the vascularisation of the liver, and different patterns of enhancement are found on the basis of the dynamics of the contrast enhancement [20]. The analysis of the dynamic of contrast enhancement pattern suggests early arterial enhancement and rapid washout in primary and secondary malignant lesions of adrenal glands. A further study demonstrated overlapping features in the enhancing pattern between benign and malignant adrenal lesions, making pattern interpretation difficult [19].

In the paediatric population, this is the first pheochromocytoma evaluated with CEUS, CT and MR imaging. The lesion showed the typical early arterial enhancement pattern after contrast-enhanced CT imaging. On MR imaging, the lesion demonstrated features of a pheochromocytoma with hyperintensity signal on T2w sequences and avidity of gadolinium-based contrast agent on T1w sequences in early phase. On CEUS we found an early arterial pattern of contrast enhancement, which mirrored the findings on the CT and MR imaging examinations, the traditional mode of imaging for these lesions, neither able to distinguish benign and malignant lesions. However, the CEUS examination allowed a real time evaluation of the perfusion pattern of the adrenal lesion, and the ability to observe all phases of the contrast examination to provide information on vascular architecture of target tissue, without the risks of irradiation of CT or the sedation required for an MR examination.

In the present report a congruency of CT, MR and CEUS findings was demonstrated, encouraging the off-label use of CEUS in the paediatric population as an imaging method with no ionizing radiation for identifying suspicious appearances of the adrenal gland; further studies are necessary to establish a role of CEUS in the diagnosis of benign and malignant adrenal lesions.

Conflict of interest Faise Al Bunni, Annamaria Deganello, Maria E. Sellars, Klaus-Martin Schulte Mudher Al Adnani, Paul S. Sidhu declare that they have no conflict of interest related to this paper.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). All patients provided written informed consent to the publication of this paper and to the inclusion in this article of information that could potentially lead to their identification.

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