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REVIEW

The good, the bad, and the ugly: uncommon CT appearances of pheochromocytoma

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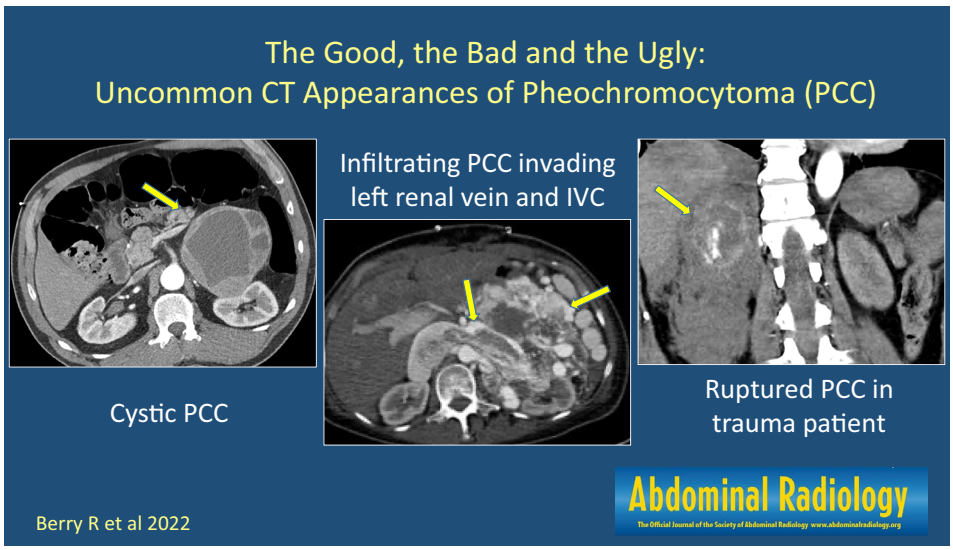
Abstract

Pheochromocytoma is a neuroendocrine tumor arising in the adrenal medulla with varied imaging appearances and associated risk of serious cardiovascular complications if left undiagnosed and untreated. It is discovered incidentally in up to 70% of cases due to the increase in use of CT in clinical practice. Biopsy can have life-threatening consequences, so imaging is crucial for diagnosis and surgical planning. The purpose of this review is to demonstrate unusual CT appearances of pheochromocytoma and enhance diagnostic confidence in cases discovered incidentally. High level of suspicion for pheochromocytoma based on CT findings, along with urinary metanephrine levels, can obviate the need for additional expensive imaging.

Graphical abstract



Keywords Pheochromocytoma · Neuroendocrine tumor · Cystic pheochromocytoma · CT appearances of pheochromocytoma

Introduction

Pheochromocytoma is a rare neuroendocrine tumor arising in the adrenal medulla, which accounts for elevated blood pressure in a small minority of adults with hypertension and is benign in 90% of cases [1–3]. Nonetheless, identification is important because uncontrolled

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catecholamine secretion increases the risk of serious cardiovascular complications [4, 5]. Approximately 11–21% of patients are asymptomatic [6], while others may present with symptoms mistaken for underlying cardiovascular conditions (e.g., palpitations) [3]. Given the protean clinical presentation and exponential growth of CT scanning, most pheochromocytomas are now identified incidentally [7, 8]. Once suspected on CT, definitive diagnosis relies on clinical and biochemical confirmation, as biopsy can prove catastrophic [9]. The most reliable indicator is urinary 24-h fractionated metanephrine level with a sensitivity of 90–97% and specificity of 69–98% [10, 11].

Notwithstanding the important role that imaging plays in the detection of unsuspected pheochromocytoma, CT diagnosis can be challenging because of the wide range of imaging appearances [12, 13]. The purpose of this pictorial essay is to demonstrate a series of pheochromocytomas that deviate from the classic finding of a solid hypervascular mass. The aim is to familiarize radiologists with the spectrum of CT appearances, facilitate efficient diagnosis through laboratory testing, and potentially obviate additional expensive imaging for further characterization.

Classic pheochromocytoma: pearls and pitfalls

The classic pheochromocytoma is a round or oval, hypervascular, heterogeneously enhancing mass (Fig. 1). The early intense enhancement is reportedly due to its capillary-rich framework [12]. Vascular pheochromocytomas can exceed washout thresholds on adrenal protocol CT and be mistaken for a lipid-poor adenoma [14, 15]. Accordingly, adrenal protocol CT washout is not reliable for distinguishing these two pathologies. If the venous enhancement level exceeds 130 HU (Fig. 2), the lesion is more likely a pheochromocytoma [14]. If the adrenal mass is detected incidentally on arterial phase CT, arterial phase attenuation of 110 HU or higher (Figs. 1, 2) is not typical of adenoma but is characteristic of pheochromocytoma. Arterial phase enhancement of > 110 HU was 58% sensitive and 100% specific for pheochromocytomas in one study [16].

Small pheochromocytoma

According to the World Health Organization classification of adrenal medullary nodules, nodules less than 1 cm,

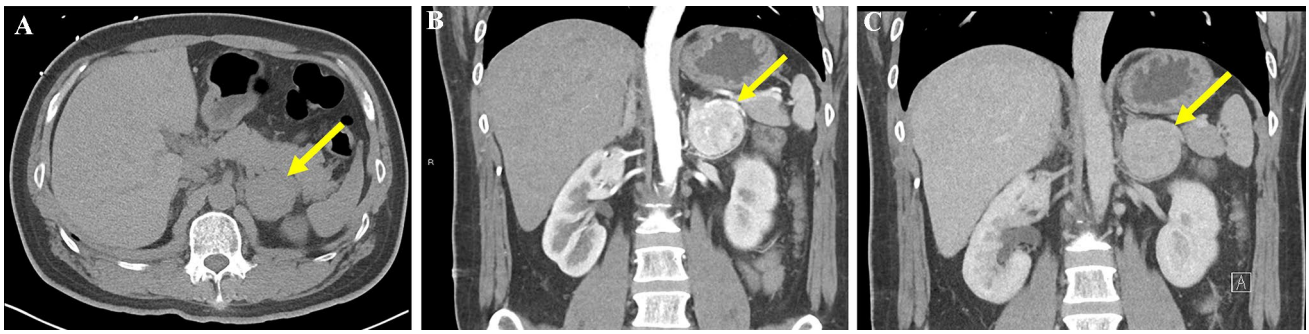

Fig. 1 Classic pheochromocytoma. Left adrenal pheochromocytoma in patient who presented with history of hypertension. Axial noncontrast (**A**), coronal arterial phase (**B**), and coronal venous phase (**C**) images demonstrate a 5.0 cm vascular mass (arrow) in the left adrenal gland, with peak enhancement on arterial phase (precontrast 42 HU, arterial phase 139 HU, and venous phase 85 HU)

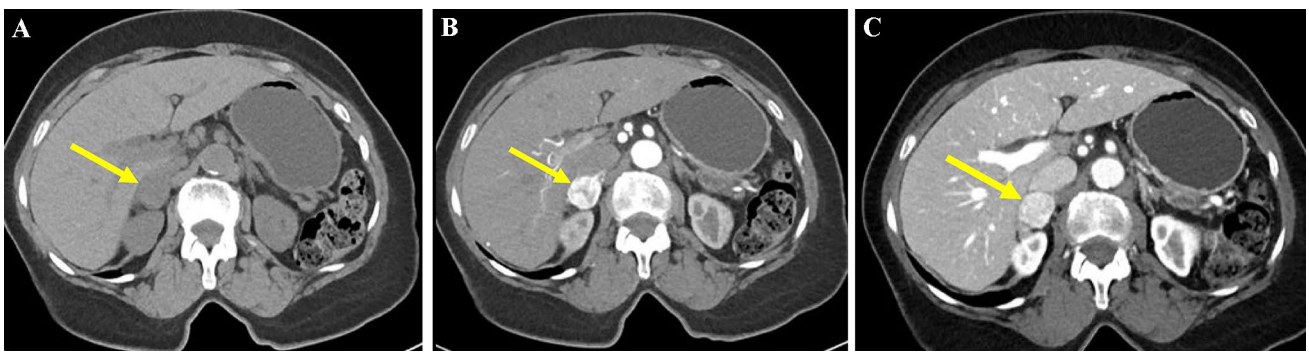

Fig. 2 Hypervascular right adrenal pheochromocytoma on dual-phase CT. Axial noncontrast (**A**), arterial phase (**B**), venous phase (**C**), CT demonstrate a 2.5 cm right adrenal mass (arrow) with attenuation of 31 HU on precontrast phase, 190 HU on arterial phase, 256 HU on venous phase

which were previously considered to be hyperplastic nodules, are now considered small pheochromocytomas based on molecular findings [17] (Figs. 3, 4). Understanding that unsuspected pheochromocytomas can be very small is a caveat to the Centers of Medicare and Medicaid Services Merit-Based Incentive Payment System (CMS MIPS) measure that advises against recommending follow-up for incidental adrenal nodules less than 1 cm [18].

Cystic or necrotic pheochromocytoma

As pheochromocytomas enlarge, the masses tend to undergo ischemia and necrosis, which accounts for central degeneration and fibrosis, reflected as heterogeneous enhancement on CT (Fig. 5) [19]. Predominantly cystic pheochromocytoma is rare but is the result of the same pathophysiology of hemorrhagic degeneration and/or necrosis (Fig. 6) [20]. The "ring sign," defined as a hyperenhancing rim, is fairly characteristic of a cystic

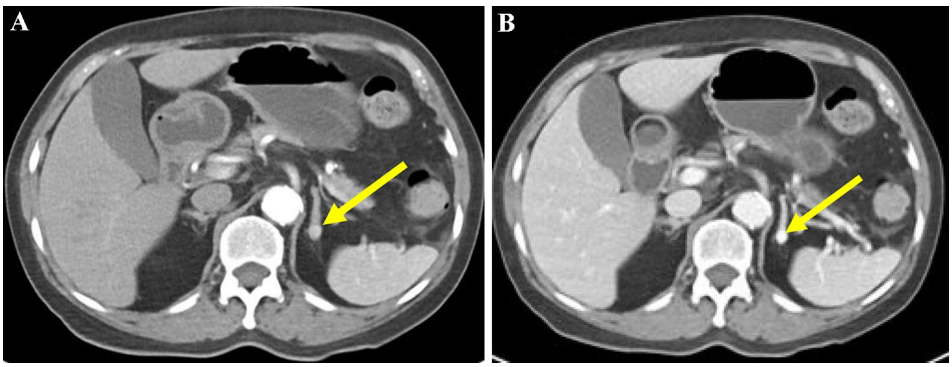

Fig. 3 Subcentimeter (9 mm) left adrenal pheochromocytoma (arrow) with high venous phase enhancement on dual-phase IV contrast-enhanced axial CT images. Attenuation of 129 HU on axial arterial phase image (**A**) and 224 HU on axial venous phase image (**B**)

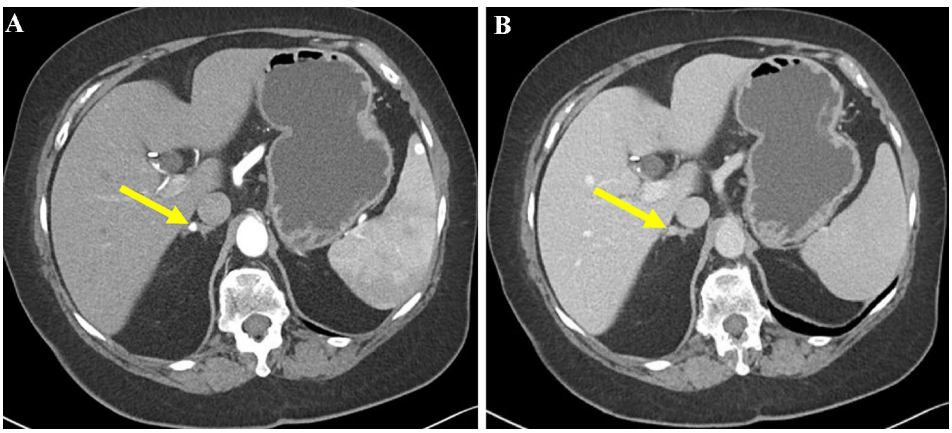

Fig. 4 Subcentimeter (6 mm) right adrenal pheochromocytoma (arrow), which enhances to 152 HU on the axial arterial phase image (**A**) and 115 HU on axial venous phase (**B**), where the nodule is subtle

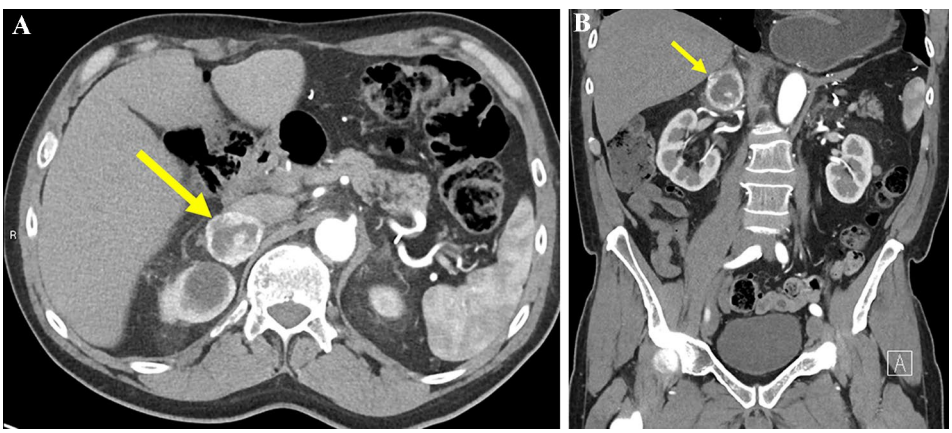

Fig. 5 Axial (**A**) and coronal (**B**) arterial phase CT images showing a 4 cm heterogeneously enhancing right adrenal pheochromocytoma (arrow) with solid components demonstrating arterial and venous phase attenuation of 144 HU and 154 HU, respectively, and central areas of low attenuation due to necrosis and degeneration

pheochromocytoma and was observed in more than 40% of cases in one series [21]. A cystic pheochromocytoma can be distinguished from other cystic adrenal masses (pseudocysts, lymphangiomas) due to variable degrees of complexity, such as a thick enhancing wall (Figs. 7, 8). In contradistinction, adrenal pseudocysts resulting from prior hemorrhage demonstrate a thin uniform wall that can be calcified. Pheochromocytoma may also present as a multiloculated cystic mass with septations (Figs. 7, 8).

Bilateral pheochromocytoma

Pheochromocytomas have the highest heritability among all endocrine tumors, with nearly 35–40% being hereditary in origin [22, 23]. The occurrence of bilateral pheochromocytomas is 10% in sporadic cases, 50–80% in multiple endocrine neoplasia type II (MEN2), and 40–80% in Von Hippel–Lindau (VHL) [22]. In patients with bilateral pheochromocytoma, a syndromic cause should be considered, most common being MEN2A or MEN2B, neurofibromatosis type 1 (NF-1) (Fig. 9), and hereditary pheochromocytoma

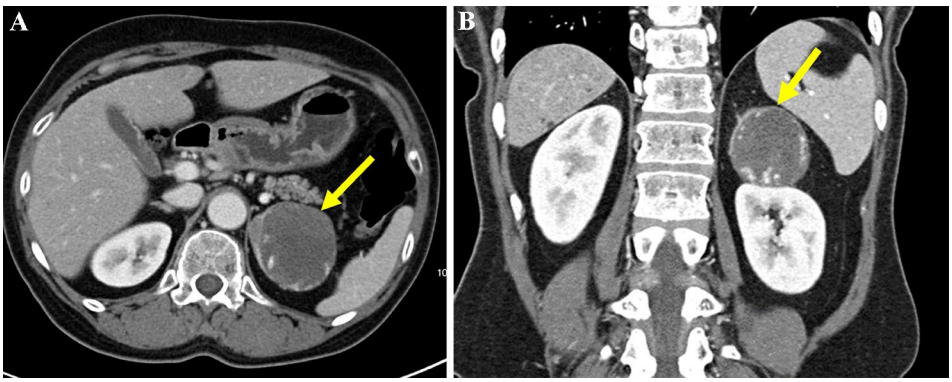

Fig. 6 Cystic pheochromocytoma—axial (**A**) and coronal (**B**) arterial phase CT showing a 6 cm cystic left adrenal mass (arrow) with peripheral rim of enhancement and a characteristic "ring sign"

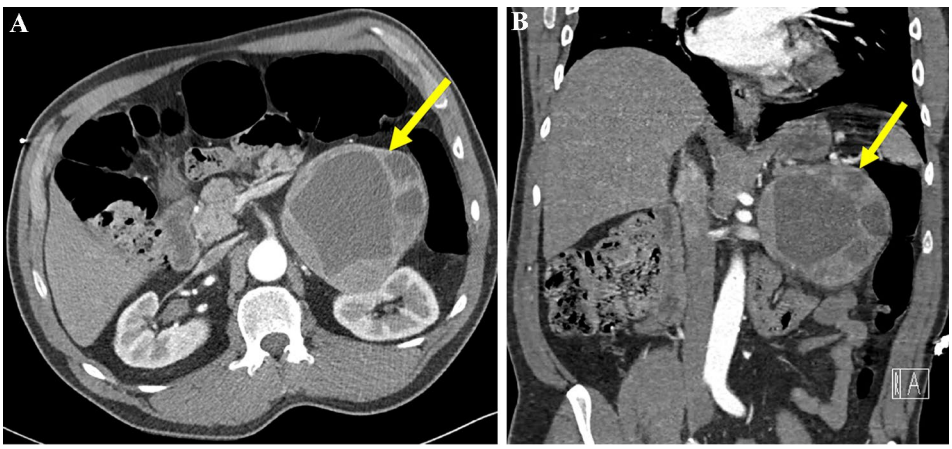

Fig. 7 Cystic pheochromocytoma. Axial (**A**) and coronal (**B**) CT showing a 10 cm complex cystic left adrenal mass (arrow) in a patient who presented with history of headache, palpitations, hypertension, diaphoresis, and elevated metanephrine levels. Symptoms resolved after adrenalectomy

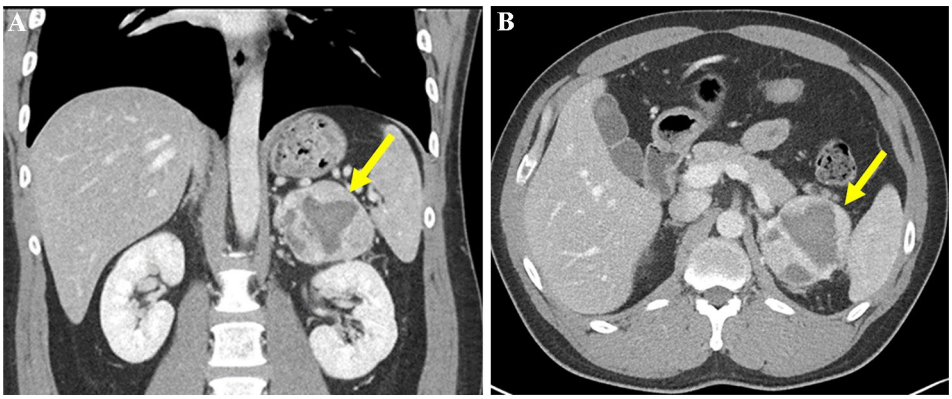

Fig. 8 A 7 cm left adrenal cystic pheochromocytoma (arrow) detected incidentally on CT done for RLQ pain. Arterial phase coronal (**A**) and venous phase axial (**B**) CT images performed prior to surgery show peripheral hyperenhancement with arterial phase attenuation of 157 HU (**A**), venous phase attenuation 105 HU (**B**), and central low attenuation of 50 HU representing necrosis and cystic changes

paraganglioma (HPP) syndrome (Fig. 10) [24]. HPP syndrome is characterized by rare benign tumors of the neural crest usually seen along the paravertebral axis from the skull base to the pelvis, and these patients can also develop renal cancers, gastrointestinal stromal tumors (GIST), and pituitary adenomas [24]. VHL is a syndrome characterized by multisystem benign and malignant tumors such as central nervous system and retinal hemangioblastomas, pheochromocytoma, renal cell carcinoma (Fig. 11), pancreatic cyst, pancreatic neuroendocrine tumor, endolymphatic sac tumor, and epididymal and broad ligament cystadenomas [25].

Infiltrating pheochromocytoma

Pheochromocytoma can present as an infiltrating suprarenal or perirenal mass (Figs. 12, 13). Infiltrating margins and invasion of local structures are not indicators of malignancy [26]. No recognized histological system defines the

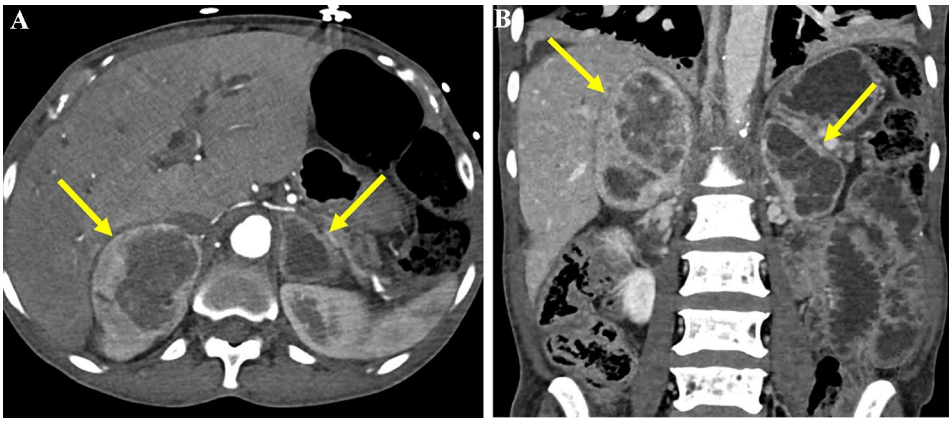

Fig. 9 Bilateral pheochromocytomas (arrow) in a patient with neurofibromatosis-1 (NF-1) who presented with abdominal pain. Axial arterial (**A**) and coronal venous (**B**) phase CT images demonstrate an 8 cm complex cystic right adrenal mass with peripheral arterial phase enhancement of 178 HU, and a 5.5 cm left adrenal cystic mass with peripheral arterial phase enhancement of 145 HU

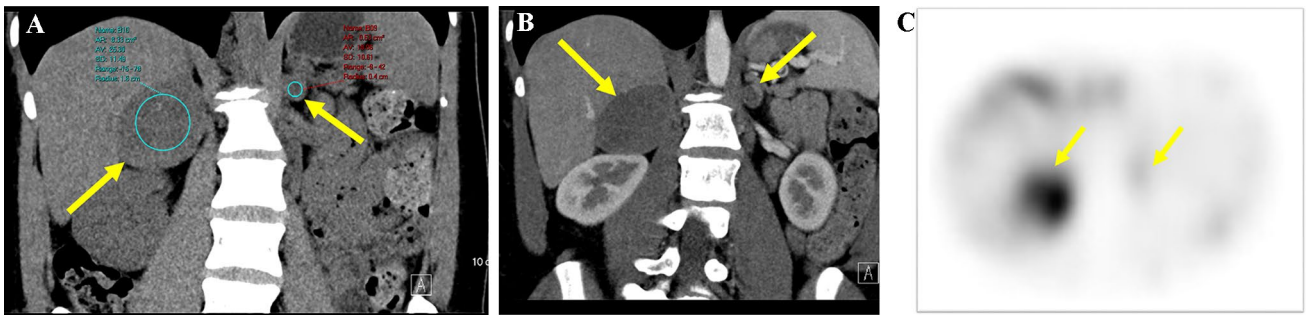

Fig. 10 Patient with palpable abdominal mass. Coronal unenhanced (**A**) and coronal venous phase (**B**) CT images show bilateral adrenal masses (6.5 cm right adrenal mass and 1.4 cm left adrenal mass—arrows) which demonstrate precontrast attenuation in the range of 20–25 HU, with intense uptake in the right adrenal mass and mild uptake in the left adrenal mass on I-123-MIBG scan (**C**). Bilateral adrenalectomy confirmed bilateral pheochromocytomas, and genetic testing consistent with Hereditary Pheochromocytoma Paraganglioma (HPP) Syndrome

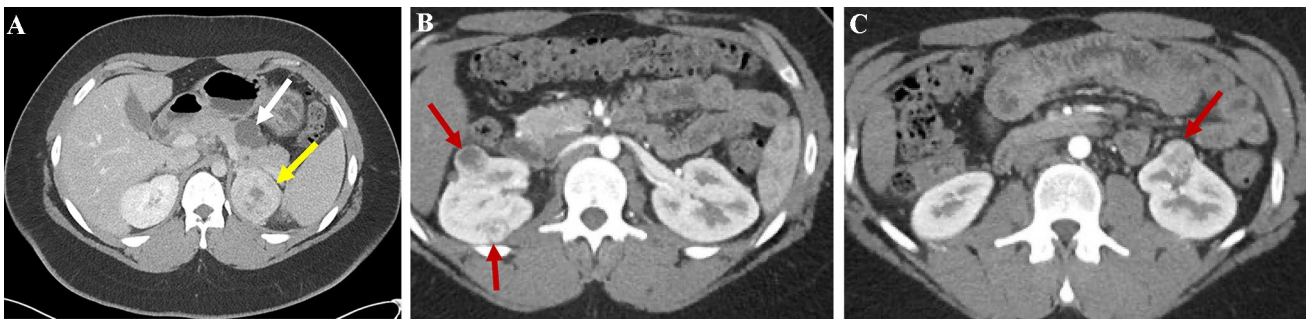

Fig. 11 Von Hippel–Lindau Disease. Axial venous phase CT (**A**) and arterial phase (**B**, **C**) demonstrate a 6 cm left adrenal pheochromocytoma (yellow arrow), bilateral multiple renal cell carcinoma (red arrows), and pancreatic cyst (white arrow)

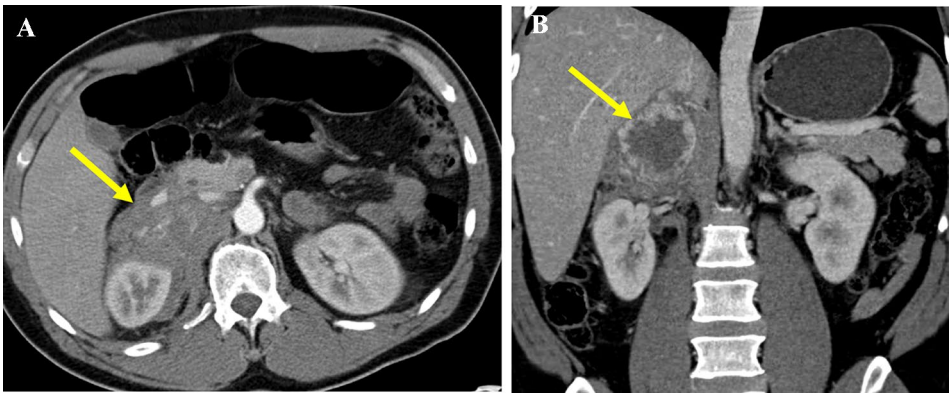

Fig. 12 Infiltrating pheochromocytoma. Axial (**A**) and coronal (**B**) CT images show a 5.5 cm right adrenal mass (arrow) with perirenal infiltration, confirmed at adrenalectomy

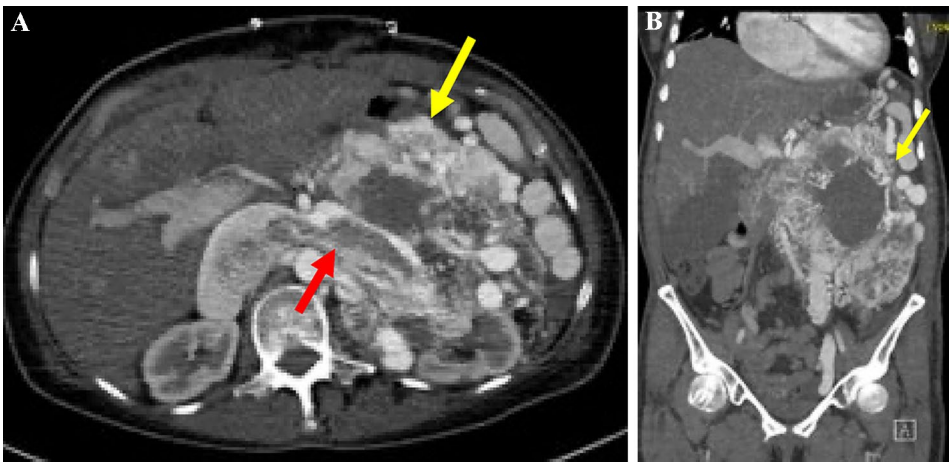

Fig. 13 Infiltrating left adrenal pheochromocytoma in a patient who presented with neck bruit. Axial (**A**) and coronal (**B**) CT images show a 19.5 cm infiltrating left adrenal pheochromocytoma (yellow arrow) with intense peripheral enhancement up to 219 HU and central necrosis invading the left renal vein and IVC (red arrow)

biological aggressiveness of pheochromocytomas. Hence, all pheochromocytomas are considered to have metastatic potential according to the fourth edition of the World Health Organization classification of endocrine tumors, which has replaced the term 'malignant' with 'metastatic' for this group of tumors [17, 27]. Approximately 5 to 10% of pheochromocytomas metastasize [15]. Differential diagnosis for this infiltrative growth pattern includes adrenocortical carcinoma, exophytic renal mass, lymphoma, and metastatic disease. Clinical presentation and biochemical testing will be essential in differentiating these diagnostic possibilities.

Metastatic pheochromocytoma

It is important to note that metastatic, aggressive, and recurrent paragangliomas are associated with SDHB gene mutation. Extraadrenal pheochromocytomas are more likely to be malignant, approximately 29–40% [15, 23]. Typical features suggestive of aggressiveness are large size, extraadrenal origin, and high levels of catecholamines in blood or urine [16, 23, 28]. As no CT features of the mass are 100% specific for malignancy, the only reliable criterion according to the World Health Organization definition is distant metastasis (Fig. 14) [17]. Therefore, the role of CT is crucial in detecting distant metastasis to make a diagnosis of metastatic pheochromocytoma. Approximately 10–30% of patients with pheochromocytomas have been found to have metastasis [29].

Pheochromocytoma with hemorrhage

Bleeding and rupture of a pheochromocytoma (Fig. 15) is rare [30], with approximately 50 reported cases between 1950 and 2000 [31]. While the exact mechanism of bleeding and rupture in a pheochromocytoma is unknown, it is believed to be associated with an increase in intracapsular pressure, due to various factors, such as trauma. Additional causes include rapid tumor growth, which can result in the tumor outgrowing its blood supply, leading to central necrosis and hemorrhage [32]. In addition, systemic hypertension due to the elevated catecholamines secreted by the tumor leads to vasoconstriction in the central vessels of the tumor, resulting in necrosis. Also, alpha-1 adrenergic blockers used to treat hypertension associated with pheochromocytoma account for intratumoral hemorrhage and avascular necrosis by lowering systemic blood pressure, which in turn causes

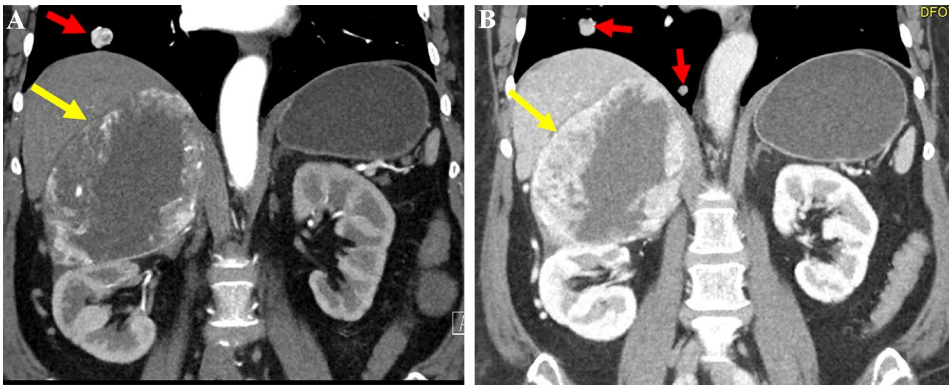

Fig. 14 Metastatic pheochromocytoma in a hypertensive patient with elevated metanephrines. Coronal arterial (**A**) and venous phase (**B**) CT images show a 12 cm right adrenal pheochromocytoma (yellow arrow) and lung metastases (red arrow). The adrenal mass demonstrates peripheral arterial enhancement of 120 HU and venous phase enhancement of 148 HU with central necrosis

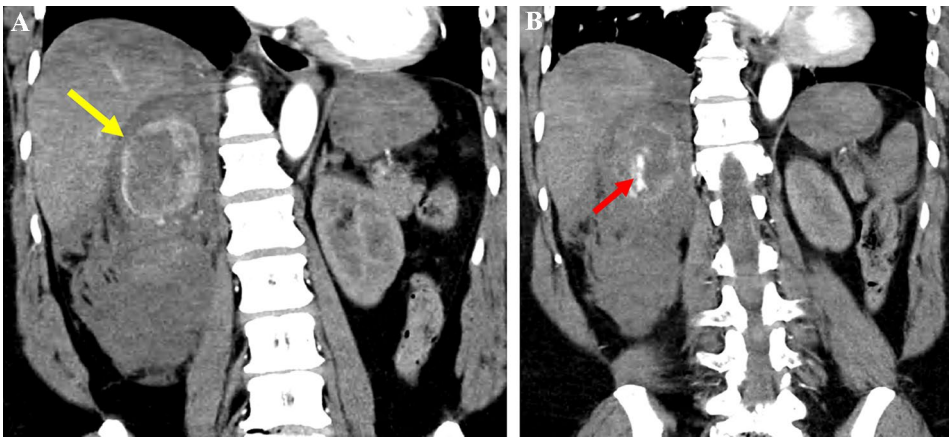

Fig. 15 Coronal venous phase contrast-enhanced CT images show an incidentally detected right adrenal pheochromocytoma (yellow arrow in **A**) that ruptured with active bleeding (red arrow in **B**) following a motor vehicle accident

vasodilatation within the tumor and subsequent engorgement and interstitial hemorrhage, thus increasing intracapsular pressure [32–35].

Intratumoral hemorrhage and rupture cause a large amount of catecholamines to be released into the circulation triggering a hypertensive crisis, severe headache, abdominal pain, ileus, sweating, and elevated serum creatinine levels [30]. Therefore, accurate and timely diagnosis is essential for the management of a life-threatening condition such as pheochromocytoma multisystem crises (PMC), in which patients present with encephalopathy, hemodynamic instability, hyperthermia, and multiorgan failure [36].

Conclusion

Diagnosis of pheochromocytoma on CT of the chest and/or abdomen is important as these tumors are often unsuspected and unrestricted catecholamine release over time results in morbidity for patients. Radiologists can facilitate diagnosis and guide management decisions by understanding the range of CT imaging features and recommending a cost-effective work up that begins with clinical assessment and laboratory tests.

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Declarations

Conflict of interest All authors declare that they have no conflict of interest.

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