BMC Endocrine Disorders

CASE REPORT

Open Access

Pheochromocytoma in a patient with heterotaxy syndrome: a case report

Farid Farahani Rad[1], Fatemeh Esfahanian[2*], Parandoosh Hashemizadeh[3] and Ehsan Mehrtabar[4]

Abstract

Background Heterotaxy syndrome is a rare congenital condition characterized by abnormal arrangement of thoracoabdominal organs, often associated with complex cardiac and splenic anomalies. Pheochromocytoma is a rare neuroendocrine tumor that overproduces catecholamines, leading to various complications. The co-occurrence of heterotaxy syndrome and pheochromocytoma has not been previously reported. This case report presents a unique finding of pheochromocytoma in a patient with heterotaxy syndrome and a functioning ectopic spleen, offering novel clinical insights.

Case presentation A 19-year-old male with congenital heart disease was incidentally found to have a right adrenal mass during abdominal ultrasonography which followed abnormal lab results. Computed tomography (CT) scans confirmed abnormal organ positioning consistent with heterotaxy syndrome, including a midline liver, right-sided colon, and the absence of a spleen in its typical location. Subsequent scintigraphy with Technetium-99 m denatured red blood cells revealed a functioning ectopic spleen in the left subdiaphragmatic space. The right adrenal mass was confirmed to be pheochromocytoma based on elevated urinary catecholamine levels. Despite recommendations for surgery, the patient chose medical management with alpha-blockers and remained stable over a one-year follow-up with no significant events.

Conclusions This case is notable concurrency of pheochromocytoma and heterotaxy and for the rare occurrence of a functioning ectopic spleen in a patient with heterotaxy syndrome, a condition where splenic anomalies typically manifest as asplenia or polysplenia. The importance of extensive imaging, particularly Tc-99 m labeled denatured erythrocyte scintigraphy imaging, is emphasized, as routine imaging like CT scans may fail to detect ectopic organs. Additionally, the concurrent presence of pheochromocytoma (PCC) and heterotaxy syndrome, although rare, raises intriguing questions about their potential link. While this case does not explore the association in detail, chronic hypoxia caused by congenital cardiovascular anomalies in heterotaxy syndrome could activate hypoxia-inducible factors (HIFs), which may promote tumorigenesis, including the development of PCC. Future studies are warranted to explore these mechanisms further and clarify the pathophysiological connection between heterotaxy syndrome, hypoxia, and PCC.

Keywords Heterotaxy, Pheochromocytoma, Adrenal mass

*Correspondence:
Fatemeh Esfahanian
fesfahanian@sina.tums.ac.ir
[1]School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Endocrinology, Vali-Asr Hospital, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
[3]Endocrinology and Metabolism Fellowship at Endocrinology Department, Imam Khomeini Medical Complex, Tehran University of Medical Sciences, Tehran, Iran
[4]Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Tehran University of Medical Sciences, Tehran, Iran

Introduction

In a normal human body, internal organs are generally arranged in a specific pattern called situs solitus, where the heart is on the left side of the chest, the liver is on the right, and other organs are positioned predictably. Heterotaxy syndrome is a rare congenital condition characterized by the disarrangement of normal thoracoabdominal structures [1]. The global prevalence of this syndrome is estimated at 1 in 10,000 to 40,000 births [2]. In individuals with heterotaxy syndrome, the usual left-right asymmetry is disrupted, leading to various anomalies in the positioning of thoracoabdominal organs affecting the heart, liver, spleen, lungs, and other organs [3]. The specific abnormalities can vary widely from person to person ranging from situs inversus which is a complete mirror image of normal thoracoabdominal structural formation and situs ambiguous defined as abnormal arrangements of thoracic and abdominal organs that is not a complete mirror image. Critical features of heterotaxy syndrome are cardiac anomalies, abdominal organ arrangement, which increases the risk of sepsis, bowel obstruction, and jaundice with additional anomalies in other parts of the body, such as limb abnormalities or abnormalities in the genitourinary system [4]. Among the symptoms and clinical features of heterotaxy syndrome, cardiac and splenic abnormalities are the most important. Cardiovascular manifestations are typically the hallmark of heterotaxy syndrome and consist of 'right atrial isomerism' and 'left atrial isomerism' which can lead to hypoxia, cyanosis, respiratory distress, and heart failure. Cyanotic congenital heart disease (CCHD) can be one of the presentations of a cardiac anomaly in heterotaxy syndrome. The usual presentation of the spleen in patients of heterotaxy syndrome are asplenia, hypoplastic spleen, and polysplenia with spleen development being almost always disrupted [5–7].

Pheochromocytoma (PCC) is a rare neuroendocrine tumor that arises from chromaffin cells of the adrenal medulla. These tumors are mainly characterized by the overproduction of catecholamines, leading to numerous symptoms and complications [8]. The annual incidence of PCC ranges between 0.2 and 0.8 per 100,000 person-years, with a prevalence between 1:2500 and 1:6500, although it is believed that PCC diagnosis is underestimated up to 50%. PCC is more common between the third and fifth decades of life. Moreover, most catecholamine-secreting tumors including PCC are sporadic and are equally common in females and males. 10–49% of these tumors are detected incidentally in imaging techniques performed for other reasons. However, 4–8% of adrenal incidentalomas are PCCs [9].

The co-occurrence of heterotaxy syndrome and pheochromocytoma is an extremely complex medical scenario and hasn't been reported before. However recent studies are suggesting the possible association between cyanotic congenital heart disease (CCHD) (that can be present in the context of heterotaxy syndrome) and PCC through various mechanisms, including hypoxia-inducible factor signaling and common genetic or developmental factors [10–13]. In this case report, we are presenting a 19-year-old male patient with the simultaneous presence of heterotaxy syndrome and PCC.

Case presentation

A 19-year-old male patient with a congenital heart defect was accidentally diagnosed with a right adrenal mass two years ago when he underwent abdominal ultrasonography (US) examination due to abnormal lab results, PT = 54.1, PTT = 45, INR = 9.65, Hb = 23.6 gr/dL, HCT = 74.4%, during his routine check-ups. The abdominal US report stated a larger than normal malpositioned liver with normal echogenicity, prominent hepatic veins suggesting hepatic congestion, gallbladder with normal size, volume, and wall thickness, normal diameter of common bile duct and intrahepatic ducts, kidneys with increased parenchymal echogenicity, lack of spleen in the usual anatomical site, and a 45*30 mm right supra-renal mass with hyper-echogenicity.

The adrenal mass had not been followed up until he was admitted to our center with no chief complaints other than occasional shortness of breath. His blood pressure was in the normal range and never exceeded 110/80 in his hospitalization period. His only medications were aspirin 80 mg/day and propranolol 20 mg/BID which were prescribed previously by a cardiologist.

At the age of five, he underwent cardiac surgery using the bidirectional-bilateral Glenn shunt procedure. Two years ago, transthoracic echocardiography (TTE) showed visceroatrial situs ambiguous and D-malposition of great arteries; the aorta was located anterior and rightward of the pulmonary artery (PA). Both great arteries arose from the right ventricle (DORV), and functionally, the right ventricle was a systemic ventricle with severe enlargement and moderate systolic dysfunction (RVEF = 40%). The TTE also revealed aortic insufficiency (AI), unbalanced atrioventricular septal defect (AVSD), large inlet ventricular septal defect (VSD), Large primum atrial septal defect (ASD), and another large secundum ASD. The common atrioventricular (AV) valve presented multiple mild to moderate regurgitations.

Diagnostic Assessment

The clinical examination revealed peripheral cyanosis, digital clubbing, and a left parasternal systolic murmur. To investigate the reported adrenal mass, firstly an abdominal ultrasonography and then a spiral computed tomography (CT) scan of the abdomen and pelvis, both with and without intravenous contrast, was performed.

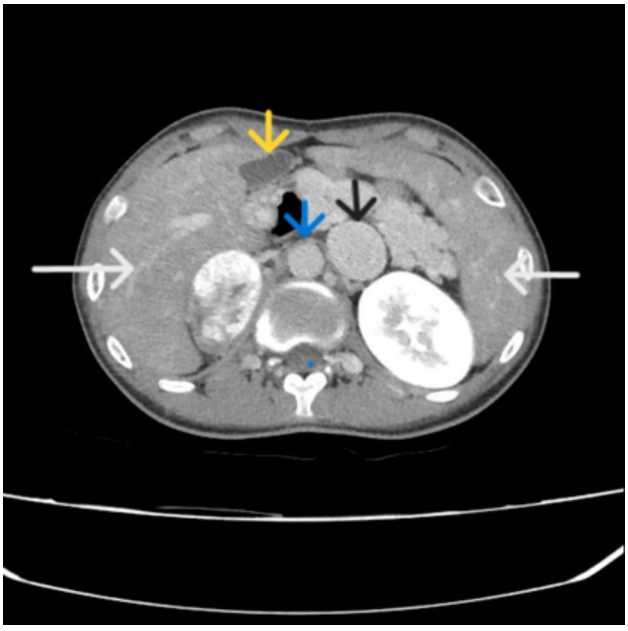

Fig. 1 Axial CT shows midline liver (white arrows), aorta (blue arrow), IVC (black arrow), and gallbladder (yellow arrow)

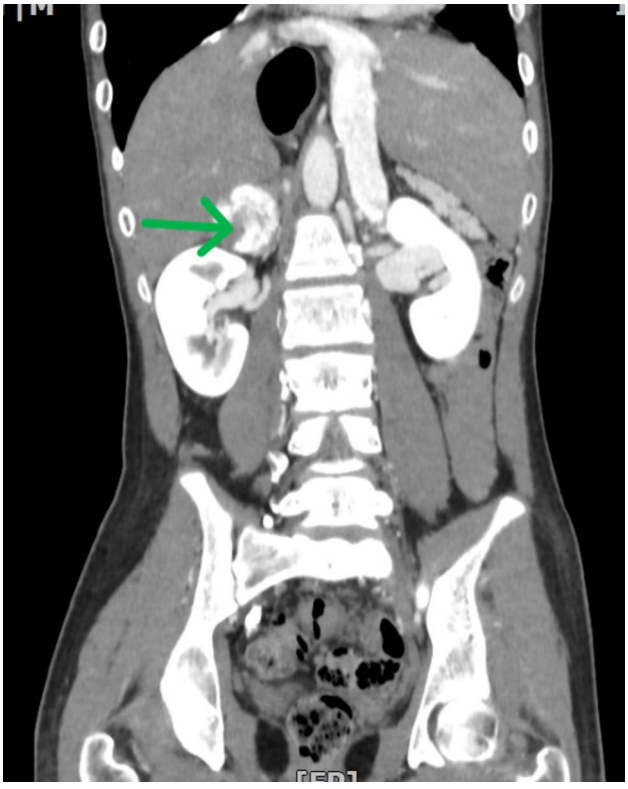

Fig. 2 Right adrenal mass (white arrow)

The abdominal US report indicated a midline positioned liver with normal parenchymal echogenicity in conjunction with a gallbladder with normal volume, no associated wall thickening, normal intra/extrahepatic ducts, and without any evidence of stones; spleen wasn't seen in its normal anatomical position implying a right-side isomerism. Moreover, a heterogenic hyper-echogenicity mass with vascularity measured at 32*50 mm was seen in the right adrenal.

Furthermore, The CT scan report stated the midline positioning of the liver, gall bladder, and stomach, the absence of the spleen, a left-sided inferior vena cava (IVC), and a right-sided aorta, collectively suggesting heterotaxy syndrome (Figs. 1 and 2). The sigmoid and descending colon were located on the right side, the ascending colon was on the left side parallel to the descending colon, and the cecum was found to be in the central part of the pelvis. The loops of the small intestine were all situated on the left side of the abdominopelvic cavity. Additionally, A right adrenal gland mass measuring 50 × 40 mm was observed, which contained calcified foci. The lesion had a density of 36 Hounsfield Units (HU) in the non-contrast images, and it demonstrated strong and heterogeneous enhancement up to 165 HU in the arterial and portal phases. In delayed images taken after 16 min, the lesion reached 98 HU, corresponding to a relative washout of 40% and an absolute washout of 52%. Despite the degree of washout, the significant enhancement in the portal phase favored a diagnosis of pheochromocytoma or malignant lesions. In addition to these possible diagnoses, high HU can be observed in extramedullary hematopoiesis. On the other hand, myelolipoma diagnosis is excluded by high HU [14].

A 24-hour collection of urine-fractionated metanephrines and catecholamines, a sensitive and specific test, was conducted to confirm the presence of pheochromocytoma. The patient's 24-hour urine metanephrine, normetanephrine, and vanillylmandelic acid (VMA) levels were measured twice, with a two-week interval between tests. The first test showed levels of 238 µg/day (1.32 µmol/day; reference range: ≤350 µg/day or ≤ 1.96 µmol/day), 2777 µg/day (15.27 µmol/day; reference range: ≤600 µg/day or ≤ 3.32 µmol/day), and 7.2 mg/24hrs (37.8 µmol/24hrs; reference range: ≤13.6 mg/24hrs or ≤ 72.6 µmol/day). The second test showed levels of 524 µg/day (2.92 µmol/day), > 3000 µg/day (> 16.5 µmol/day), and 11.0 mg/24hrs (57.8 µmol/24hrs) respectively. These data corroborated the detection of the pheochromocytoma in the CT scan reports. Due to the economic constraints of the patient, functional imaging such as MIBG or Gallium-DOTATATE scintigraphy couldn't be performed. However, a denatured red blood cell (RBC) scintigraphy with single-photon emission computed tomography (SPECT) was performed to ensure that the mass detected on the CT scan was not a spleen and to demonstrate asplenia. Interestingly, images from Technetium-99 m-Denatured RBCs revealed normal functioning

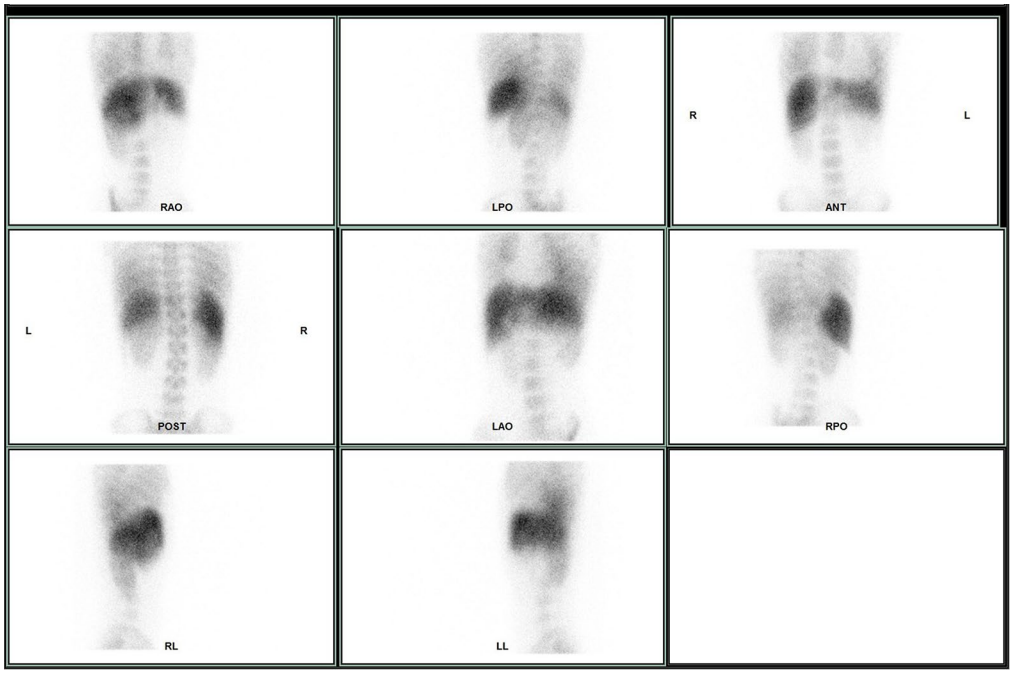

Fig. 3 Radiotracer uptake in right subdiaphragmatic space

tissues and a normal-sized liver and spleen located on the contralateral side of the abdominal cavity (Fig. 3).

Treatment

A surgical procedure was recommended to the patient. However, the patient chose to voluntarily discharge against medical advice, with a prescription for an oral α-blocker, Prazosin, at a dosage of 1 mg daily.

Outcome and follow-up

The patient was followed up for a duration of one-year post-diagnosis. Given the patient's remote location, follow-up was conducted via telephone consultations. At the time of the last follow-up, the patient was found to be in a stable general condition. He continued his prescribed medication regimen. Although the medical team insisted on performing a follow-up sonography and/or CT scan to detect any possible size changes of the mass, the patient refused to cooperate due to previously mentioned reasons.

Notably, the patient's blood pressure remained within the normal range, indicating effective management of hypertension. Throughout the follow-up period, no adverse or unanticipated events were reported.

Discussion

In this case report we presented a young male with concurrent heterotaxy syndrome and pheochromocytoma. The patient had evident cyanotic features on physical examination but no adrenergic symptoms and the right adrenal mass was found incidentally in abdominal ultrasonography, which was performed as a part of his abnormal laboratory results workup. As for the follow-up of the adrenal mass, an IV-contrast abdominal CT scan showed multiple abnormalities in the positioning of the intra-abdominal organs, as described above. The adrenal mass features favored pheochromocytoma, a diagnosis confirmed by elevated urinary catecholamines. Although no apparent structure as a spleen was seen in the abdominal CT scan, a denatured RBC scintigraphy with SPECT revealed a spleen in the right subdiaphragmatic space. Based on these findings, the presented case was diagnosed as situs ambiguous (a manifestation of heterotaxy syndrome where, unlike situs inversus, the thoracoabdominal structures are not strictly mirrored) with pre-existing cyanotic congenital complex heart disease and pheochromocytoma. Additionally, erythrocytosis which is a secondary phenomenon associated with chronic cyanosis, was observed in this case, as well as high false positive clotting measurements which are seen in high hematocrit levels [15].

Reticuloendothelial cells (RE cells) have phagocytic properties. They are located in a few organs, such as the bone marrow, the liver, and the spleen. leveraging their phagocytic property, we can use radio-labeled particles such as Tc-99 m sulfur colloids and Tc-99 m denatured RBC to evaluate and image these organs. Tc-99 m denatured RBC is acquired from normal red blood cells adequately denatured to be spherocytes, which are larger in particle size (also larger than Tc-99 m sulfur colloids), so most of them are exclusively trapped by the spleen and this imaging modality is considered the most specific

imaging modality for evaluation of spleen [16]. Tc-99 m labeled denatured erythrocyte scintigraphy allows diagnosis confirmation demonstrating phagocytic ability in the ectopic spleen tissue [17]. Two cases of accessory spleen misdiagnosed as atypical pheochromocytoma were reported before [18, 19], so we decided to perform a denatured RBC scintigraphy for our patient to ensure he had no spleen. However, scintigraphy revealed a functioning right-sided spleen, which was not reported on the CT scan review. This finding underscores the importance of extensive imaging for complex medical scenarios.

Currently, there is no medical literature and genetic knowledge that supports any link between heterotaxy syndrome and pheochromocytoma, as previously established, cardiac malformations are a major and consistent finding in Heterotaxy syndrome cases. These abnormal cardiac developments can lead to hypoxia and cyanosis which was evident in our case. Moreover, many solid tumors, including pheochromocytoma, are characterized by a hypoxic state. Hypoxia has been shown to promote both tumor progression and resistance to therapy through hypoxia-inducible factors (HIFs) which are the primary mediators of the transcriptional hypoxic response. High levels of HIF lead to the transcription of hypoxia-responsive genes, which are involved in tumorigenesis [10, 12, 13]. CCHD in heterotaxy syndrome is responsible for the hypoxic state of the patients. This inducing effect and the strong link between CCHD and PCC have been demonstrated previously [10, 11]. This hypothesized pathophysiological pathway can be a possible mechanism for the concurrency of heterotaxy syndrome (which has a main cardiac malformation component) and pheochromocytoma which necessitates a comprehensive and separate investigation.

According to existing literature that investigated the genetic mutations responsible for heterotaxy syndrome, several genes such as NODAL, ZIC3, and LEFTY2 contributed to heterotaxy syndrome development. On the other hand, mutations for several specific genes including VHL, SDHA, and MEN2 A/B led to pheochromocytoma. Unfortunately, genome sequencing was not performed in our case due to economic obstacles, but further genetical investigations can be beneficial in identifying possible common pathogenesis pathways of these diseases [9, 20].

Although a case report of an 11-year-old boy with Ivemark syndrome characterized by asplenia, congenital heart anomalies, and abnormal abdominal organ placement, in conjunction with pheochromocytoma has been reported before [21], to our knowledge, this case report is the first of its kind in terms of reporting a heterotaxy syndrome in conjunction with pheochromocytoma in a young adult. More interestingly in contrast to the majority of heterotaxy syndrome patients which manifest asplenia (lack of spleen and absence of spleen functionality), hypoplastic spleen, or polysplenia (more than one splenic mass), our case presents with a well-functioning right-sided single spleen which was discovered in Tc-99 m labeled denatured erythrocyte scintigraphy imaging.

Coming to study limitations, pheochromocytoma confirmatory functional imaging such as MIBG or Gallium-DOTATATE scintigraphy couldn't be performed due to the economic status of the patient. Although ultimately our medical team proposed the compensation for imaging, but the patient refused to be admitted again for further follow-up and additional imaging. furthermore, follow-up sonography and/or CT scan for detecting changes in mass dimensions wasn't possible due to the lack of cooperation of the patient and being in a remote location thus having limited access to robust imaging facilities. The same reasons prevented the deployment of the optimal treatment plan which was surgery of the adrenal mass. More importantly, a thorough genetic assessment would have been useful in detecting mutations responsible for patients' complex diagnosis.

Our takeaway from this extremely rare case is that physicians should pay attention to the possible underlying disorders that can decompensate the cardiovascular status of the heterotaxy patient. In this case, pheochromocytoma in conjunction with possible paroxysmal or sustained hypertension could in theory lead to decompensation of already compromised normal cardiac functionality. In heterotaxy patients with an abdominal mass, pheochromocytoma could be considered a possibility thus an accurate diagnosis of pheochromocytoma in the context of heterotaxy syndrome can prevent further cardiac decompensation thereby reducing morbidity and mortality.

Abbreviations

PCC	Pheochromocytoma
CCHD	Cyanotic congenital heart disease
CT	Computed tomography
HIFs	Hypoxia-inducible factors

Acknowledgements
None.

Author contributions
All authors made individual contributions to authorship and reviewed and approved the final manuscript. F.F.R: Writing the main manuscript - Review & Editing, Manuscript submission F.E: Conceptualization, Supervision, diagnosis, and management of this patient P.H: Writing - Original Draft, Investigation E.M: Data Collection.

Funding
No public or commercial funding.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This case report was conducted in accordance with the ethical standards of Tehran University of Medical Sciences and adhered to the principles outlined in the Declaration of Helsinki. The need for formal ethics approval was waived due to the nature of the case report, which involved a retrospective review of clinical data without experimental interventions. Written informed consent was obtained from the patient for the publication of this case and any accompanying images. All identifying information has been anonymized to protect the patient's privacy.

Consent for publication
Signed informed consent was obtained directly from the patient.

Clinical trial number
Not applicable

Competing interests
The authors declare no competing interests.

Received: 2 October 2024 / Accepted: 31 December 2024
Published online: 10 March 2025

References

1. Kim SJ. Heterotaxy syndrome. Korean Circ J. 2011;41(5):227–32.
2. Lin AE, Krikov S, Riehle-Colarusso T, Frías JL, Belmont J, Anderka M, et al. Laterality defects in the national birth defects prevention study (1998–2007): birth prevalence and descriptive epidemiology. Am J Med Genet A. 2014;164a(10):2581–91.
3. Lagrotta G, Moises M. Heterotaxy Polysplenia Syndrome in Adulthood: focused review and a Case Report. Cureus. 2020;12(1):e6822.
4. Kothari SS. Non-cardiac issues in patients with heterotaxy syndrome. Ann Pediatr Cardiol. 2014;7(3):187–92.
5. Jacobs JP, Anderson RH, Weinberg PM, Walters HL 3rd, Tchervenkov CI, Del Duca D, et al. The nomenclature, definition and classification of cardiac structures in the setting of heterotaxy. Cardiol Young. 2007;17(Suppl 2):1–28.
6. Loomba R, Shah PH, Anderson RH, Arora Y. Radiologic considerations in Heterotaxy: the need for detailed anatomic evaluation. Cureus. 2016;8(1):e470.
7. Agarwal R, Varghese R, Jesudian V, Moses J. The heterotaxy syndrome: associated congenital heart defects and management. Indian J Thorac Cardiovasc Surg. 2021;37(Suppl 1):67–81.
8. Pacak K. New Biology of Pheochromocytoma and Paraganglioma. Endocr Pract. 2022;28(12):1253–69.
9. Aygun N, Uludag M. Pheochromocytoma and paraganglioma: from epidemiology to clinical findings. Sisli Etfal Hastan Tip Bul. 2020;54(2):159–68.
10. Jones RB Jr., Cohen DL. Congenital Cyanotic Heart Disease and the Association with Pheochromocytomas and Paragangliomas. Curr Cardiol Rep. 2023;25(11):1451–60.
11. Opotowsky AR, Moko LE, Ginns J, Rosenbaum M, Greutmann M, Aboulhosn J, et al. Pheochromocytoma and paraganglioma in cyanotic congenital heart disease. J Clin Endocrinol Metab. 2015;100(4):1325–34.
12. Jochmanová I, Yang C, Zhuang Z, Pacak K. Hypoxia-inducible factor signaling in pheochromocytoma: turning the rudder in the right direction. J Natl Cancer Inst. 2013;105(17):1270–83.
13. Richter S, Qin N, Pacak K, Eisenhofer G. Role of hypoxia and HIF2α in development of the sympathoadrenal cell lineage and chromaffin cell tumors with distinct catecholamine phenotypic features. Adv Pharmacol. 2013;68:285–317.
14. Khater N, Khauli R. Myelolipomas and other fatty tumours of the adrenals. Arab J Urol. 2011;9(4):259–65.
15. Marlar RA, Potts RM, Marlar AA. Effect on routine and special coagulation testing values of citrate anticoagulant adjustment in patients with high hematocrit values. Am J Clin Pathol. 2006;126(3):400–5.
16. Lake ST, Johnson PT, Kawamoto S, Hruban RH, Fishman EK. CT of splenosis: patterns and pitfalls. Am J Roentgenol. 2012;199(6):W686–W93.
17. Graziani T, Baldari G, Sammartano A, Scarlattei M, Migliari S, Pescarenico MG, et al. SPECT/CT with 99mTc labelled heat-denatured erythrocyte to detect thoracic and abdominal splenosis. Acta Biomed. 2020;91(4):e2020098.
18. Xia Z, Zhou Z, Shang Z, Ji Z, Yan W. An unusual right-sided Suprarenal accessory spleen misdiagnosed as an atypical pheochromocytoma. Urology. 2017;110:e1–2.
19. Kim MK, Im CM, Oh SH, Kwon DD, Park K, Ryu SB. Unusual presentation of right-side accessory spleen mimicking a retroperitoneal tumor. Int J Urol. 2008;15(8):739–40.
20. Pereira BD, Luiz HV, Ferreira AG, Portugal J. Genetics of Pheochromocytoma and Paraganglioma. Codon; 2019. pp. 1–22.
21. Latendresse TR, Goldin AB, Jonmarker C. Anesthesia for pheochromocytoma resection in a child with Fontan circulation. Can J Anaesth. 2011;58(7):642.

Publisher's note