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CASE REPORT

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Paragangliomas and syringomyelia in Tetralogy of Fallot—A case report and literature review

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Key Clinical Message

Pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries, paragangliomas, and syringomyelia are uncommon diseases. Furthermore, in the absence of any genetic link and with less than five reported adult patients surviving unrepaired rare form of Tetralogy of Fallot, our case shows noteworthiness. The possibility of definitive treatment of these conditions is rendered unsafe due to this persistent defect. Thus, management and ongoing survival of this patient remains complex and challenging.

KEYWORDS

22q11DS, carotid body tumor, cyanotic congenital heart disease, PA/VSD/MAPCAs, succinate dehydrogenase complex subunit D mutation, syringomyelia

1 | INTRODUCTION

Cyanotic congenital heart disease (CCHD) accounts for 25% of all congenital heart defects.[1] Pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries (PA/VSD/MAPCAs) is a rare and complex entity of CCHD[2]; it is considered an extreme form of Tetralogy of Fallot (TOF). CCHD occurs usually sporadically but can be associated with genetic syndromes.[1] The link between congenital heart defects and chromosome 22q11.2 deletion syndrome (22q11DS), also known as DiGeorge or velocardiofacial syndrome has been well established; up to 64% of these syndromic patients are diagnosed with congenital heart disease.[3] Several other features including anatomical and vascular anomalies of the head and neck, CNS abnormalities, endocrine disorders and immune deficiency have also been observed.[3,4] Neuroendocrine tumors such as paragangliomas (PGLs)

are regarded as separate entities, arising from paraganglial cell clusters. Head and neck PGLs (HNPGLs) are also uncommon neuroendocrine tumors with a 35%–40% predisposition to hereditary disease.[5,6] Amongst all types of HNPGLs, around 60% comprise carotid body tumors (CBTs). In the familial form of the disease, the most frequently mutated gene is the Succinate Dehydrogenase Complex Subunit D (*SDHD*) gene; this mutation leads to paraganglioma syndrome type 1 (PGL1).[6] Consequently, this syndrome has also never been related to congenital heart disease or neurological developmental defects. We describe a patient with unrepaired PA/VSD/MAPCAs and HNPGLs along with 2 other conditions with an attempt to establish a possible genetic association that could explain the etiology.

2 | CASE PRESENTATION

We present a case of a 34-year-old male Czech patient with a history of unrepaired PA/VSD/MAPCAs that was referred to us for a painless slow growing lump on the left side of the neck, lasting for 1.5 years. He had no relevant family history. The diagnosis of his rare CCHD was made at the age of 3 months, when he underwent several investigations including diagnostic catheterization. He was found to have pulmonary atresia with non-confluent pulmonary artery, non-restrictive ventricular septal defect and four major aortopulmonary collateral arteries (two collaterals bilaterally) as well as central cyanosis. The defect was left unrepaired, in accordance with his parent's wishes, leading to the development of pulmonary hypertension during early childhood; thus, making it remarkably unsafe to repair at a later stage. This cardiovascular defect led to severe polycythemia and hyperviscosity syndrome. Here, we show a CT Angiography with the presence of multiple major aorto-pulmonary collateral arteries (MAPCAs) taking off from the aortic arch and descending aorta (Figure 1). The ECHO (Figure 1) showed good function of both ventricles, right ventricular dilatation and hypertrophy, non-restrictive ventricular septal defect with absence of left ventricular outflow obstruction but significantly enlarged aorta. The lump in the neck was discovered during his regular cardiology follow-ups, where he is being managed conservatively.

On clinical examination at the otorhinolaryngology department, the patient had central cyanosis and finger clubbing in addition to a pulsatile palpable mass of approximately 40 × 40 × 30 mm along level II on the left side of the neck (Figure 1) with restrictive craniocaudal movement. He had no associated dysphagia, dyspnea or dysphonia or other cranial nerve defects.

2.1 | Diagnostic assessment

An ultrasound of the neck showed a solid hypervascular spherical mass of 36 × 36 × 38 mm in the carotid bifurcation with hypoechogenic islands on the left side; a similar mass of 20 × 13 × 25 mm was also noted on the right carotid bifurcation. The patient underwent CT and confirmatory MRI of the neck (Figure 1). Clinical findings and diagnostic imaging done in 2017 were in accordance with the findings of CBTs bilaterally. The tumor on the left side was classified as Shamblin III and the right one as Shamblin I. A ^{18}F-FDOPA PET/CT confirmed the findings and ruled out the presence of other paragangliomas or pheochromocytoma. Biochemical tests showed normal plasma metanephrine (0.063 nmol/L), normetanephrine (0.308 nmol/L) and chromogranin A (32.7 ng/mL) levels.

Informed consent for genetic analysis was obtained and peripheral venous blood sample was collected accordingly. This was done to identify any germline pathogenic variants that could possibly contribute to these rare syndromic presentations. Single nucleotide pleomorphisms array was negative for the deletion mutation on chromosome 22q11.2. Next generation sequencing examining the entire panel of paraganglioma/pheochromocytoma related genes and subsequently, whole exome sequencing revealed the absence of any well-known germline pathogenic variants related to the presence of cardiac abnormalities and/or paragangliomas.

2.2 | Treatment

The safety in the surgical management of CBTs with a persistent VSD and pulmonary hypertension has not been established yet. Furthermore, surgery under general anesthesia and the potential risk of infection could significantly worsen his condition. Therefore, it was decided to adopt the 'wait and scan' approach for his CBTs.

2.3 | Outcome and Follow-up

During his review appointment in 2021, he complained of an unusual swelling on his left forearm with no pain or paresthesia. Clinically, there was a pulsatile soft tissue mass 80 × 30 mm with obvious bruit on auscultation on the radial aspect of the proximal forearm. Ultrasound and MRI of the arm revealed a vascular lesion in the lateral antebrachial region (Figure 2) of 79 × 29 × 19 mm with radiological characteristics comparable to paraganglioma. This lesion is closely followed-up after consultation with vascular surgeons. Later, MRI of the cervical and thoracic

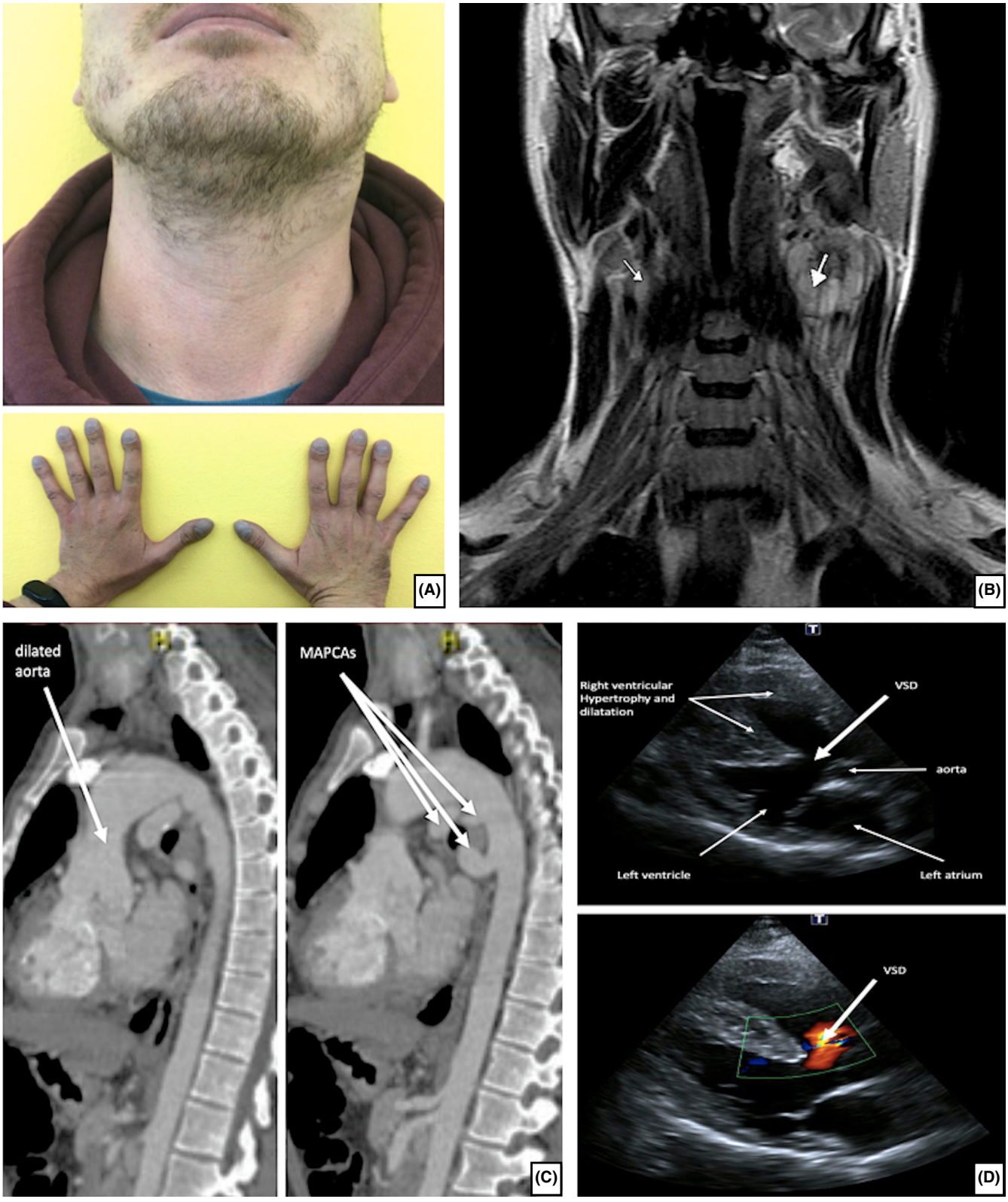

FIGURE 1 (A) Frontal view of neck (above) showing bilateral neck mass and dorsal view of hands (below) with finger clubbing. (B) Coronal T2W MRI of the neck demonstrating bilateral CBTs (arrows). (C) Lateral CT Angiography of the chest demonstrating TOF with dilated aorta and MAPCAs. (D) Parasternal long axis view from a 2D ECHO (above) with color flow doppler (below) demonstrating intracardiac defects associated with TOF.

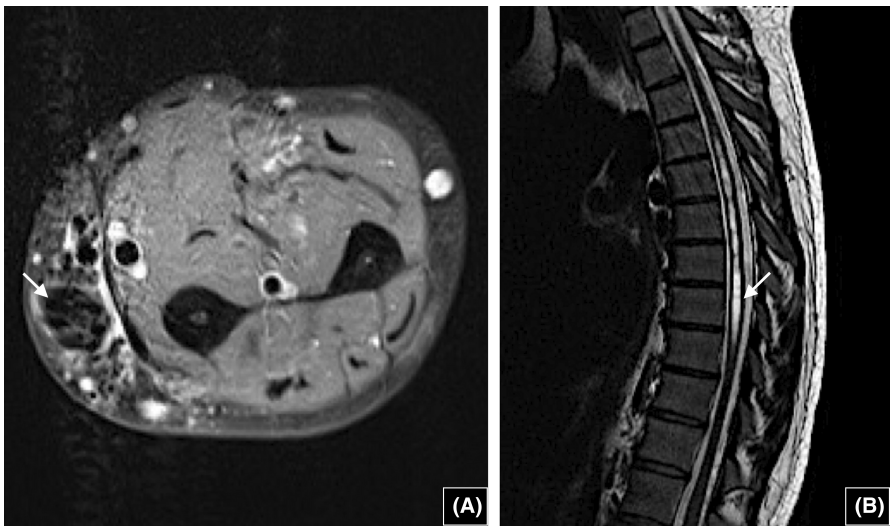

FIGURE 2 (A) Axial T1W gadolinium MRI of the forearm demonstrating the tumor. (B) Sagittal T2W MRI of the thoracic spine showing syringomyelic cavity at the level of Th3-Th11.

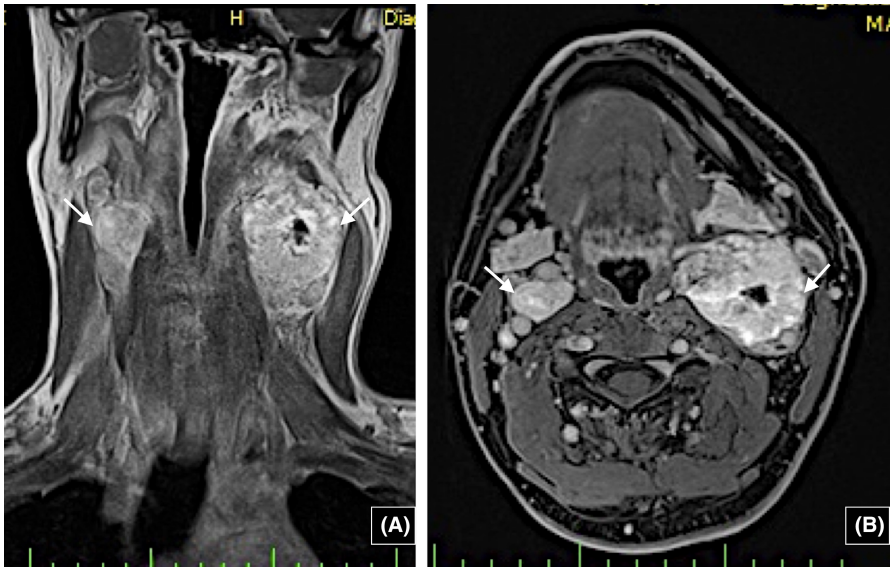

FIGURE 3 (A) Coronal and (B) axial T1W MRI of the neck demonstrating progression of CBTs.

spine showed the presence of a syringomyelic cavity extending from Th3-Th11 (Figure 2) with maximum cavity width of 6 mm observed at the level Th8. He was referred to a neurologist for further consultation. No intervention was planned since he had no accompanying symptoms.

Annual MRI scans of the neck showed minimal progress of disease over the first 4 years, but significant progression of the carotid body PGLs was noted from 2022 (Figure 3) onwards; therefore, after discussion with the patient, we planned to proceed with radiotherapy of the neck tumors. Pretreatment MRI neck, done in early 2023, showed Shamblin III 49 × 39 × 60 mm on the left side and Shamblin I 23 × 14 × 25 mm on the right side. In May 2023, he underwent 26 fractions of radiotherapy with a total dose of 45 Grays without significant complications. The follow-up MRI scan of the neck in June 2024 shows slight improvement with 41 × 39 × 50 mm on the left side and 13 × 12 × 21 mm on the right side.

3 | DISCUSSION

Our patient presented with uncorrected PA/VSD/MAPCAs, which is rarely seen. Presentation is dependent on the adequacy of pulmonary blood flow via aorto-pulmonary collaterals and can range from cyanosis, cardiac murmurs to heart failure, usually in infants. Timing is crucial in the treatment of such defects, otherwise deterioration in cardiopulmonary physiology related to growth and hypoxemia restricts intervention.[2] As already mentioned, CCHD has been well documented with 22q11DS; albeit the rarity of PA/VSD/

MAPCAs, one study showed 57% of 45 patients with PA/VSD/MAPCAs had the syndrome.[7] An array of symptoms affecting multiple organs can arise due to microdeletion mutation in 40 established genes. Mutations of the *TBX1* and *WNT5* genes that are located on the chromosome 22q11.2 comprise cardiovascular defects.[8] A mutation of the *TBX1* gene can also be related to defects in the central nervous system including a developmental form of syringomyelia (associated with Chiari Type I malformation).[9,10] In the absence of acquired etiology or hereditary cause, it can be assumed that our patient probably has an idiopathic form. Along with motor disorders, swelling on the arm with sensory deficit has been seen with syringomyelia.[11] Our patient presented with swelling of the forearm only, the radiological findings corresponded to a well-defined hypervascular tumor in the antebrachial region; differential diagnosis includes arteriovenous, venous, capillary, and lymphatic malformations.[12] Despite the unusual location, the possibility of paraganglioma cannot be entirely disregarded.[13,14] Treatment varies from observation to highly invasive amputation surgery.[12]

HNPGLs are mostly non-secreting tumors and often discovered incidentally on imaging or due to compression symptoms.[5] Patients with CBTs typically present with a painless, slowly enlarging mass in the lateral part of the neck, as seen in our patient. Dysphagia, dysarthria, dysphonia (deficits of the IX–XI, XII cranial nerves), as well as Horner syndrome and syncope may be seen with advancing tumor size. Bilateral tumors are seen in only 10% of patients. HNPGLs have not been directly associated with 22q11DS. Bilateral CBTs strongly supports the presence of a germline pathogenic variant, frequently related to the *SDHD* gene, located on chromosome 11q.23. Abnormalities of the cardiovascular or nervous systems have not been observed with PGL1.[6] However, among the other gene mutations leading to HNPGLs, the von Hippel–Lindau (*VHL*) gene, linked to the VHL syndrome, can also be considered. This is located on chromosome 3p25.3; the subtypes include a vast range of tumors including central nervous system,[5] and syringomyelia has also been reported.[15] It should also be mentioned that a mutation in the tumor suppressor gene, *SMARCB1*, located on chromosome 22q11.2, can lead to aggressive head and neck tumors.[8] None of the conditions in our patient were related to a pathogenic genetic mutation.

In the absence of any such genetic link, the development of CBTs could be attributed to a physiological response to chronic hypoxemia, a stimulus for carotid body hypertrophy. This connection explains the increased incidence of both hyperplasia and neoplastic transformation. Consequently, high altitude habitation and CCHD are precipitating factors for the formation of CBTs[16–19]; the later posing a much higher risk[20,21] (Table 1). Uncorrected pulmonary atresia with ventricular septal defect also leads to profound hypoxemia, thus supporting the theory of development of CBTs in our patient.

The survival rates of PA/VSD/MAPCAs have been significantly improved with midline unifocalization approach in comparison to the untreated natural history, when 20-year survival was 20%.[2,22] Adult survivors of this condition without surgical intervention are quite rare and dependent on the adequacy of pulmonary blood flow derived from aortopulmonary collateral vessels. Well-developed MAPCAs may have the greatest contribution to survival exceeding three decades.[23] Disease-specific survival for patients with HNPGLs, even with large primary tumor, is comparable to the general population.[24] Depending on the size of the larger CBT, preoperative embolization and surgical removal is the preferred procedure, nonetheless in patients with uncorrected CCHD, it poses a high risk of worsening cardiopulmonary physiology. If bilateral CBTs are left untreated for long periods, there are risks of developing pressure symptoms from the growing tumors and multiple cranial nerve dysfunction leading to devastating consequences: hence radiotherapy was administered.

TABLE 1 Chronic hypoxia and bilateral CBTs.

Study	Patients with CBTs	% with bilateral CBTs	Influence of high altitude	Presence of CCHD	Type of CCHD
Saldana et al.[16]	23	4.3	+	–	–
Rodriguez-Cuevas et al.[17]	120	5	+	–	–
Pacheco-Ojeda et al.[18]	229	7.9	+	–	–
Wang et al.[19]	122	19.7	+	–	–
Hirsch et al.[20]	1	100	–	+	Common ventricle with high pulmonary vascular resistance
Opotowsky et al.[21]	2	50	–	+	TOF with pulmonary stenosis

Abbreviations: CBT, Carotid body tumor; CCHD, congenital cyanotic heart disease.

4 | CONCLUSION

The absence of any genetic association could signify that the formation of bilateral CBTs is attributed to the profound hypoxemia caused by the uncorrected CCHD and the development of syringomyelia is simply idiopathic. Despite the unexpected anatomical location, the possibility of a paraganglioma in the forearm cannot be excluded from the clinico-radiological correlation. Nevertheless, tumor tissue, when available should be analyzed using molecular testing. In conclusion, this could be categorized as a very rare case of a patient surviving with uncorrected PA/VSD/MAPCAs and bilateral CBTs in combination with possibly unrelated uncommon diseases.

AUTHOR CONTRIBUTIONS

Anasuya Guha: Conceptualization; data curation; methodology; project administration; visualization; writing – original draft. **Petra Antonova:** Formal analysis; investigation; resources; writing – review and editing. **Tomas Zelinka:** Investigation; methodology; resources; writing – review and editing. **Ales Vicha:** Investigation; methodology; resources; software; validation; writing – review and editing. **Karel Pacak:** Formal analysis; investigation; supervision; writing – review and editing. **Martin Chovanec:** Data curation; funding acquisition; project administration; validation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

STUDIES INVOLVING HUMAN SUBJECTS

All procedures performed in studies involving human subjects were in compliance with the Helsinki declaration and further in accordance with local ethical guidelines of the institutional ethical committees of Charles University, Prague, Czech Republic.

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