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20 Years of Good Quality of Life in a Patient with Paraganglioma Harboring a Germline SDHB Large Deletion

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Abstract

Context: Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are neuroendocrine neoplasms that can be caused by heterozygous germline loss-of-function mutations in SDHx genes. The phenotypic differences between the syndromes derived from the various mutations in the SDH complex are not completely understood.

Case description: The authors report a case of a 22-year-old female patient with a functioning extra adrenal PGL, which predominantly released noradrenaline and dopamine. The diagnosis was done after a hypertensive crisis that required hospitalization in an Intensive Care Unit. Abdominal computed tomography (CT) showed a 4cm mass in the lower inferior para-aortic region, suggestive of PGL. She underwent a laparotomy for removal of the mass and histopathological examination confirmed the diagnosis of PGL. This patient has been followed for the last 20 years with laboratory and imaging exams without showing recurrence of disease. A genetic screening recently performed showed that she harbors a germline pathogenic large deletion of succinate dehydrogenase complex subunit B (SDHB) gene. This deletion is identical and shares the same haplotypic background as the one reported in Portuguese PGL patients.

Conclusion: We report a symptomatic PGL patient with a surprisingly benign evolution for a long time, despite harboring a germline SDHB mutation that is associated with more aggressive clinical presentation, course, and lethality. The other interesting aspect of this case is the possible link of the mutation to a founder effect.

Key words: SDHB; Germline-mutation; Extra Adrenal Paraganglioma

Introduction

Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are neuroendocrine neoplasms derived from the chromaffin tissue of the adrenal medulla or from extra-adrenal sympathetic and parasympathetic paraganglia [1].They can be caused by hetero-zygous germline loss-of-function mutations in SDHx genes [2,3].

The succinate dehydrogenase (SDH) enzyme complex acts on the Krebs cycle by catalyzing the conversion of succinate to fumarate with the reduction of ubiquinone to ubiquinol via the mitochondrial respiratory chain. The flavoprotein SDHA and the iron sulphur protein SDHB are responsible for the SDH catalytic process, while SDHC and SDHD act as anchorage proteins [4].

The phenotypic differences between the syndromes derived from the various mutations in the SDH complex are not completely understood, although some have proposed that mutations involving SDHA and SDHB subunits are likely to result in total loss of function, thus leading to more aggressive forms of the disease, unlike mutations in SDHC and SDHD subunits [3-5].

We report a case of a patient with PGL, who harbors a pathogenic germline deletion of SDHB. Clinical, laboratory, treatment and follow up data are discussed.

Case presentation

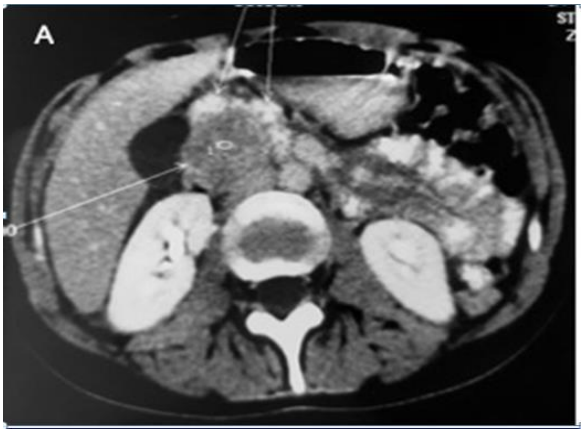
A 22-year-old woman, descendant from Portuguese and Italians, was referred to our Endocrinology Department with an abdominal computed tomography (CT) showing a mass of 4 cm in the greatest diameter, located in the lower inferior para-aortic region in Zuckerkandl organ, suggestive of PGL (Figure 1).

Her story called attention to episodes of holocranial headache and intense sweating since she was 17 years old. Two months before her consultation, she presented to the Emergency with hypertensive crises,

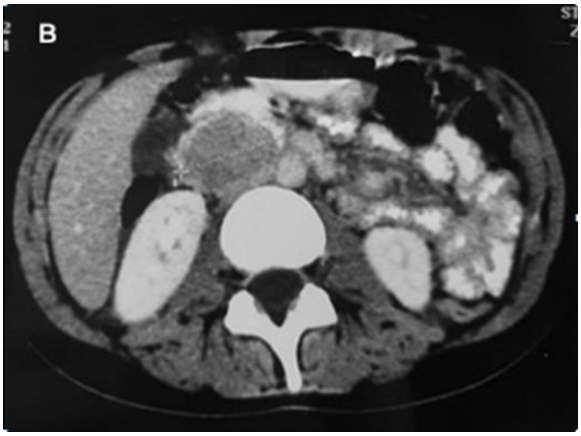
accompanied by tachycardia, profuse cold sweating, nausea, vomiting, and dyspnea, leading to hospitalization in an Intensive Care Unit. Other complaints were oliguria, weight loss, insomnia, hypermenorrhea and anxiety. A previous echocardiogram showed mild left ventricular hypertrophy. There were no similar cases in her family history.

Figure (1): Contrast enhanced CT scan showing:

(A) The retroperitoneal mass with peripheral moderate enhancement, in close relation with second and third portions of duodenum (superior white arrows)



(B) The neoplasm had approximately 4 cm in maximum diameter.



Her treatment started with prazosin, followed by propranolol 2 weeks later. After normalization of blood pressure and heart rate, a laparotomy was performed to remove the mass. Histopathological examination of the surgical specimen described, at macroscopy, an encapsulated and elastic nodule measuring 40 x 30 x 30 mm. The microscopic exam showed a neoplasm of neuroendocrine lineage with cells arranged in small nests ("Zell Baden"), with richly vascularized surrounding stroma; rounded and oval neoplastic cells with broad eosinophilic, homogeneous or discretely granular cytoplasm and nuclei of different size and nucleolus not very evident; multinucleated cells were occasionally observed and mitosis were rare. The diagnostic conclusion was of PGL.

The postoperative exams showed cure of the disease (Table 1), as the patient remained stable and without recurrence 20 years after surgery. Nowadays, she is asymptomatic with normal blood pressure and the abdominal CT scan remains normal.

The patient underwent genetic screening, after giving her informed consent as established by the approval of the study by the Ethics Committee of our Institution, and was found to harbor a germline 15678bp deletion in the SDHB gene, encompassing the promoter region and exon 1 of the gene (c.-10413_73-3866del; The Human Gene Mutation Database ref. no. CG068241).

This deletion had already been reported in Portuguese PGL patients, where it appears to have a founder effect [2]. We thus assessed whether this deletion had the same haplotype background as the one described by Martins *et al* [2] by examining the same seven SNPs (rs1569754, rs3946080, rs2143811 and rs5772743, located upstream of the deletion; and rs7545518, rs7545499 and rs7536679, located downstream of the deletion).

Table (1) Pre and postoperative laboratory results.

Analyte	Preoperative results (µg/24 hours)	Post-operative results (µg/24 hours)	Reference interval
Urinary noradrenaline	2000	14	Till 80 µg/24h
Urinary adrenaline	26	1	Till 20 µg/24h
Urinary dopamine	2150	186	Till 20 µg/24h
Total methanephrines	4176	242	Till 1000 µg/24h

After selective amplification of the deleted allele we observed that the haplotype of this patient was defined by C-A-C-delA-A-A-T for the above mentioned SNPs, which matches the one detected in Portuguese patients harbouring the same deletion.

Discussion

We present a case of a patient with PGL due to a pathogenic germline deletion in the SDHB gene. Mutations in SDHB gene have been implicated as the most common cause in the pathogenesis of malignant PHEOs/PGLs in both children and adults [6], with the exception of the Dutch population, where founder mutations in SDHD are the most prevalent genetic events [7]. There is little information on the penetrance and phenotypic variability of these cases, complicating the clinical investigation and management of the carriers [8]. Independently of the genetic identification and any associated syndromes, the treatment of choice for PHEO/PGL is surgery [9,10].

This patient presented with non-specific abdominal symptoms and "spells", which led to the investigation and diagnosis of a functioning PGL. While the diagnosis of PGL was at age 22, the early symptoms probably started at age 17. The mean age at diagnosis of PGL in SDHB mutation carriers in Previous series is about 30 years old [10-12]. A study referred that the age-related penetrance for females was 5.2% at age 20 [13].

PGLs usually secrete noradrenaline, as opposed to PHEOs, where secretion of adrenaline predominates. Moreover, the high secretion of dopamine is more frequently associated with malignant lesions [4]. The patient presented preferential noradrenaline and dopamine secretion (Table 1), which is the predominate pattern of the SDHB mutation [4], but the course of the disease was benign.

Martins *et al* [2] performed a SDHx genetic screening in 37 Portuguese PGL patients and showed that 11 of them harbored the germline 15678bp deletion in the SDHB gene, encompassing the promoter and exon 1 of the gene, the same deletion present in this patient. Although the patients described by Martins *et al* were considered as sporadic cases, a subsequent analysis showed that the deleted alleles of all 11 patients shared a common haplotype, in a significantly higher frequency than in control individuals, suggesting a founder effect for this deletion, which has probably settled in the northern Portuguese/Galician populations [2]. The same deletion of SDHB exon 1 was previously detected in Iberian Peninsular people by Cascon *et al* [5]. Noteworthy, the patient here reported is of Portuguese and Italian prole

and also shares the same haplotype detected in the deleted alleles of the 11 Portuguese patients. This finding suggests that she probably inherited the deletion from her Portuguese ascendants and that she might share a common ancestor with the patients described by Martins *et al* [2].

Sympathetic PGLs develop along the sympathetic chain, extending from the skull base to the pelvis; about 75% are located in the abdominal region [5], as occurred in this patient. The SDHB gene mutation is more often associated with thoracic or abdominal extra-adrenal PGL. Multiple tumors are identified in several patients with SDHB mutations, which are also related with more aggressive tumors, younger age and a greater tendency to metastasize [10]. However, during the 20 years of follow-up, our patient did not show relapse or metastases, indicating a disease of benign behavior, unlike what is generically described in the literature, i.e. that SDHB mutations are associated with more aggressive clinical presentation, course, and lethality [13].

Conclusion

This is a patient diagnosed with symptomatic PGL and a surprisingly benign evolution for a long time, despite harboring a germline SDHB mutation, which are usually associated with a more aggressive clinical presentation, course, and lethality. Therefore, considering the limitations of drawing conclusions based on just one case, we suggest that these patients should never be abandoned and should be evaluated together with the relatives who are carriers without clinical manifestations. We discussed the clinical and laboratory aspects, as the experience in the management of the disease is relatively limited.

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Disclosure summary

The authors declare that there is no conflict of interest regarding the publication of this article. PBA and RF are employed by Diagnósticos da America SA, but the company had no interference in the development of the study and this affiliation does not alter policies on sharing data and materials.

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