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A rare case of aggressive, hereditary paraganglioma associated with a pathogenic variant in SDHD

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Paragangliomas are rare neuroendocrine neoplasms that arise from the chromaffin tissue. Tumours originating from the sympathetic nervous system are located within the adrenal medulla (pheochromocytomas) or sympathetic ganglia in the neck, chest, abdomen, and pelvis, and they usually produce catecholamines, while tumours arising from the parasympathetic nervous system are commonly found in the head, neck, and mediastinum and are usually non-secreting. Almost 40% of paragangliomas have a genetic background [1]. They can be associated with autosomal dominant inheritance mutations in one of the genes encoding succinate dehydrogenase (SDHB, SDHD, SDHC, SDHA, SDHAF2) or can coexist in genetically determined endocrine syndromes such as MEN type 2A and 2B, NF1, or VHL. Additional genes predisposing to hereditary pheochromocytoma are still being discovered that should be investigated when searching for the genetic cause of pheochromocytoma in affected families. Each of the mutated genes is associated with the specific characteristics of clinical features of the pheochromocytoma they are responsible for. Therefore, usually, the clinical picture may be an indicator of the gene that should be searched for pathogenic variants in a given patient and their family.

Herein, we present a rare case of a patient with an aggressive, metastatic, hereditary paraganglioma associated with a pathogenic variant in SDHD and an atypical clinical outcome.

A 69-year-old woman with a history of arterial hypertension and hypothyroidism (after treatment with I-131 due to hyperthyroidism) was admitted to the Department of Endocrinology in 2015 because of bone metastasis of neuroendocrine cancer from an unknown primary lesion. The patient had undergone removal of the paraganglioma of the right carotid artery in 2008, and she had had surgical treatment of an L3 vertebra fracture in 2015. During the hospitalisation, biochemical data showed a significantly increased concentration of chromogranin A 93.6 ng/mL (0–6) and increased excretion of 3-methoxytyramine 15821.6 ug/24 h (N: 0–220) in 24-hour urine collection.

The material collected from the L3 vertebral metastasis was re-examined (a diagnosis of metastatic neuroendocrine cancer was included in the primary histopathological report), and the diagnosis of metastatic paraganglioma was established. The tumour cells expressed synaptophysin and had a Ki-67 index at 9%, and no expression of somatostatin receptors was found in the neoplastic cells. An active metabolic recurrence of paraganglioma in the area of bifurcation of the common carotid artery (Fig. 1)/mandibular angle on the right side, with massive dissemination to the skeletal system (Fig. 2) and the involvement of the chest lymph nodes, were visualised in ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F] F-FDG PET-CT) (07.12.2015).

In Iodine-131-meta-iodobenzylguanidine ([^{131}I]I--MIBG) scintigraphy (23.12.2015), tracer uptake in the lower jaw area on the left side, on the neck in the thyroid gland topography to the right of the midline of the body, and xiphoid process of the sternum in the thoracic spine and the plate of the right iliac bone were found (Fig. 3).

The molecular analysis revealed an uncommon variant, c.34G>A (p.Gly12Ser), in the SDHD gene. At that time point, this variant was of unknown clinical significance. The detected variant occurred as a homozygote in Sanger sequencing analysis. Therefore, the genetic investigation was complemented by multiplex ligation-dependent probe amplification (MLPA), result-

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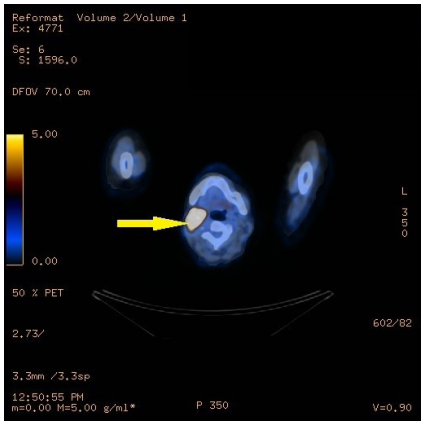

Figure 1. *PET/CT imaging with 18F FDG shows local recurrence of paraganglioma. The arrow shows an active metabolic area of paraganglioma in the area of bifurcation of the common carotid artery/mandibular angle on the right side. (Department of Endocrinology Medical College Jagiellonian University Krakow, Poland)*

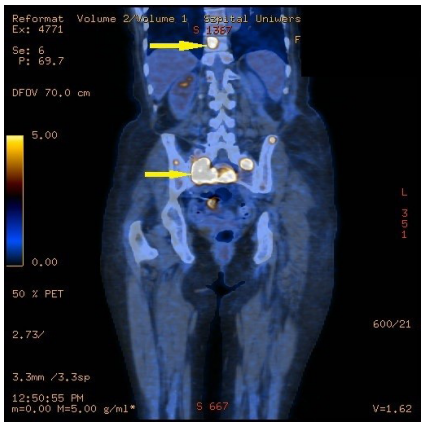

Figure 2. *PET/CT imaging with 18F FDG. The arrows show an active metabolic area of paraganglioma in the area of vertebral column and sacroiliac bone. (Department of Endocrinology Medical College Jagiellonian University Krakow, Poland)*

ing in the detection of a pathogenic alteration — an extensive gene deletion (encompassing exons 1–3) on one allele. Currently, the c.34G>A (p.Gly12Ser) variant is classified as benign or probably benign in the NCBI ClinVar database.

The patient was referred for therapy with iodine-labelled MIBG but unfortunately died due to dissemination.

Genetic testing was performed in the patient's family members. Her son inherited the extensive deletion, but because SDHD mutations are paternally inherited [2, 3], it should not be evident clinically. The molecular analysis was also conducted in his 2 children: genetic alterations were excluded in the case of his son but confirmed in the case of his daughter — the same extensive gene deletion (encompassing exons 1–3) with a high probability (approximately 80%) of causing symptoms of the paraganglioma syndrome. The daughter — a 20-year-old woman — was diagnosed with a lesion in a sternum indentation a few weeks ago and is now undergoing a diagnostic process.

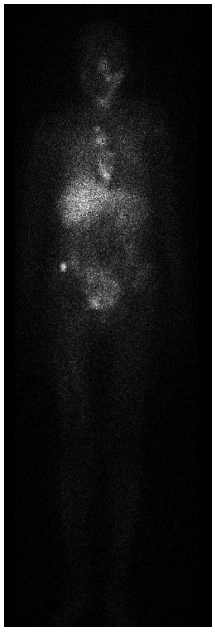

Figure 3. *SPECT/CT imaging with 131I-MIBG. Accumulation of a tracer in the lower jaw area on the left side, on the neck in the thyroid gland topography to the right of the midline of the body, and xiphoid process of the sternum in the thoracic spine and the plate of the right. (Department of Endocrinology Medical College Jagiellonian University Krakow, Poland)*

Genetic alterations in the *SDHD* gene account for approximately 9% of all pheochromocytoma/paraganglioma cases [1]. Paragangliomas associated with SDHD variants develop most often in head and neck locations, they are usually benign tumours, and the risk of metastatic disease in carriers is approximately 5–7% [4, 5]. The above case was characterised by an atypically aggressive clinical course with relapse and distant metastasis 7 years after the initial diagnosis.

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