Familial SDHC Mutation Associated With Prolactin/GH-Secreting Pituitary Adenoma and Paraganglioma

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Introduction: SDHx genes mutations are associated with hereditary pheochromocytoma and paraganglioma syndromes. We describe the very rare case of a patient with SDHC related familial paraganglioma and pituitary adenoma.

Case: A 65 year old man consulted for macroscopic hematuria. CT Scan showed a 7cm mass lateral to the right kidney invading inferior vena cava and 18F-FDG PET revealed hypermetabolism in the mass, a retroperitoneal adenomegaly and the body of L2 vertebra with spinal MRI aspect of metastasis (Figure 1). Continuous blood pressure monitoring, plasma catecholamines and their methoxylated metabolites were normal. Chromogranine-A value was 439µg/l (normal<100µg/l). Total right adrenalectomy, lumbo-aortic lymphadenectomy and nephrectomy were performed. Vertebral metastasis was treated by radiofrequency. Histopathology confirmed the diagnosis of paraganglioma with 2% mitotic index.

During follow-up, erectile disorders developed. Explorations revealed partial hypogonadotropic hypogonadism (Testosterone 214ng/dl [nle 280-820], LH 2.2mU/ml, FSH 2.5mU/ml) with hyperprolactinemia (470ng/ml, nle <19ng/ml) and elevated IGF1 (214 ng/ml, nle 41-196ng/ml for age/sex). Oral glucose tolerance test confirmed GH oversecretion. MRI showed a T2 hyperintense pituitary adenoma of 15X17mm with left cavernous sinus extension but free optic structures (Figure 2). We retained the diagnosis of Mixed Pituitary adenoma and started Dopaminergic agonist plus somatostatine analogue. Genetic revealed an unknown mutation on SDHC gene on exon 4 c239-242dupGTGC. The same mutation was found in his siblings (son, daughter and the grand son).

Discussion: SDHx genes mutations are well known causes of familial paraganglioma and pheochromocytoma (1). These mutations alter the mitochondrial complex 2, resulting in an increase in HIFa, VEGF, TGFa, and EPO that will activate cellular divisions and inactivate apoptosis. Germline SDHx mutations associated pituitary adenoma have been reported sporadically in the literature (2)(3). The specific situation of SDHC mutation associated paraganglioma and pituitary adenoma concerned just one prior case described by Jimenez E & al (4). Whether SDHx mutations are implicated partially or principally in the neoplastic process of pituitary adenomas is not fully clear. In one case of a bilateral pheochromocytoma associated GH secreting pituitary adenoma reported by Xerouki & al (5), the germlinal mutation on SDHD gene (c.298_301delACTC) was associated with a loss of heterozygosity for the SDHD genetic locus and down-regulation of SDHD protein in pituitary adenomas. Recently, two large series including 309 and 80 cases of isolated pituitary adenomas interested on their SDHA/B immunoblotting and immunocommunohistochemistry an reported a prevalence of abnormal SDHx immunostaining in 0,3% of pituitary tumors respectively (1)(6). Most of these cases were macroadenomas with higher Ki67 proliferation index compared to normal SDHx staining pituitary adenomas.

Conclusion: To our knowledge it is the second reported observation of SDHC mutation associated paraganglioma and pituitary adenoma. This case and the review of the literature suggest that SDHx gene mutation could be, in very rare cases, related to pituitary adenomas occurrence. Our patient was managed by dopaminergic agonist plus somatostatine analogues allowing the control of it’s pituitary oversecrections. The patient benefits of close follow-up for his metastatic pheochromocytoma with stable metastatic disease until now.

References:

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