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

Mohammed Barigou[1], Alexandre Buffet[1], Antoine Bennet[1], Pascal Pigny[2], Laurent Bellec [3], Philippe Caron[1], Delphine Vezzosi[1]

[1] CHU Larrey, Toulouse, France; [2]CHRU de Lille-Lille, France; [3]CHU Rangueil-Toulouse, France

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 hypermetabolisms 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 2.2mUI/ml, FSH 2,5mUI/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 complexe 2, resulting in an increase in *HIFα ,VEGF, TGFα*, 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 phechromocytoma associated GH secreting pituitary adenoma reported by Xerouki & al (5), the germinal 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 immunochemistry an reported a prevalence of abnormal *SDHx* immunostaining in 0,3 an 3% of pituitary tumors respectively (1)(6). Most of these cases were macroprolactinomas with higher Ki67 proliferation index compared to normal *SDHx* staining pituitary adenomas.

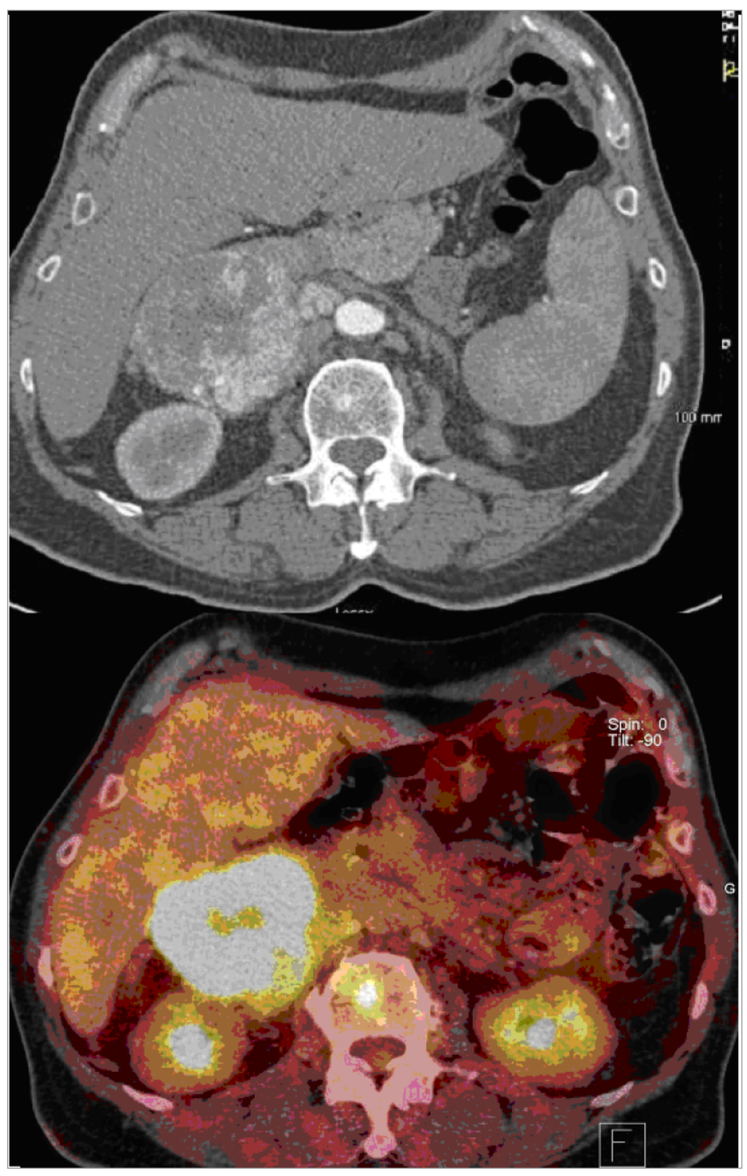

Figure 1: CT scan and PET CT (18FDG) revealing a 7cm mass (arrows) located laterally to the right kidney.

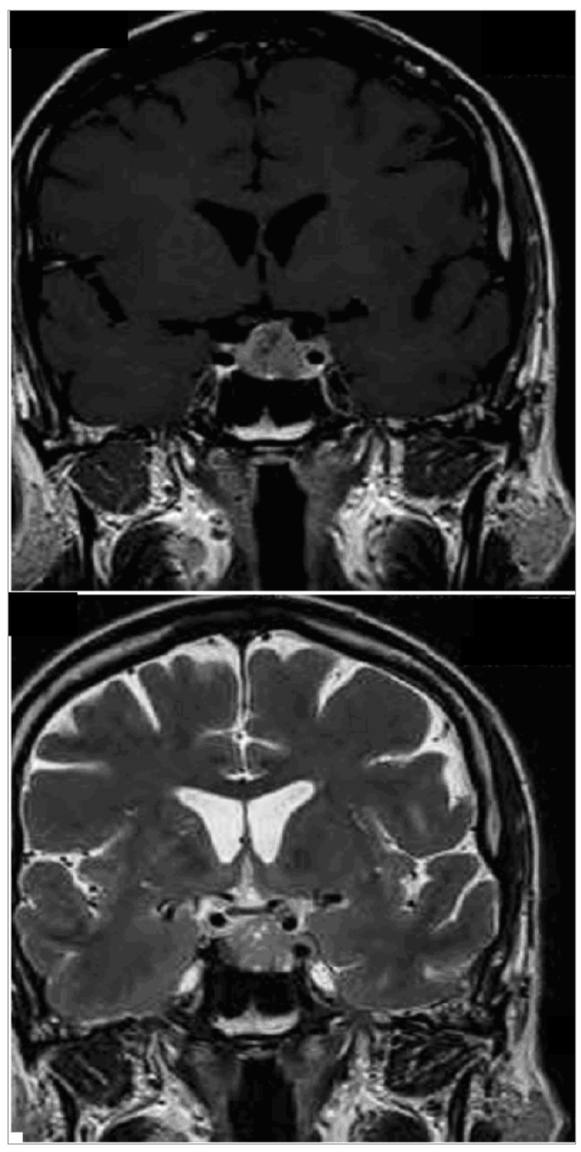

Figure 2: Pituitary MRI revealed an intrasellar lesion measuring 15X17mm with T2 hyperintense, T1 hypointense aspect and increased signal after gadolinium infusion compatible with pituitary adenoma.

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 ovesecretions. The patient benefits of close follow-up for his metastatic pheochromocytoma with stable metastatic disease until now.

References:

1. Gill AJ, Toon CW, Clarkson A, Sioson L, Chou A, Winship I, et al. Succinate Dehydrogenase Deficiency Is Rare in Pituitary Adenomas. Am J Surg Pathol. 2014 Apr;38(4):560–6.
2. Xekouki P, Stratakis CA. Succinate dehydrogenase (SDHx) mutations in pituitary tumors: could this be a new role for mitochondrial complex II and/or Krebs cycle defects? Endocr Relat Cancer. 2012 Dec;19(6):C33–40.
3. Dwight T, Mann K, Benn DE, Robinson BG, McKelvie P, Gill AJ, et al. Familial SDHA Mutation Associated With Pituitary Adenoma and Pheochromocytoma/Paraganglioma. J Clin Endocrinol Metab. 2013 Apr 30;98(6):E1103–8.
4. López-Jiménez E, de Campos JM, Kusak EM, Landa I, Leskelä S, Montero-Conde C, et al. SDHC mutation in an elderly patient without familial antecedents. Clin Endocrinol (Oxf). 2008 Dec;69(6):906–10.
5. Xekouki P, Pacak K, Almeida M, Wassif CA, Rustin P, Nesterova M, et al. Succinate Dehydrogenase (SDH) D Subunit (SDHD) Inactivation in a Growth-Hormone-Producing Pituitary Tumor: A New Association for SDH? J Clin Endocrinol Metab. 2012 Mar;97(3):E357–66.
6. Andrews, MD E, Stacey Mardekian MD, Miettinen M, Mark Curtis MD. Succinate Dehydrogenase Deficiency in Sporadic Pituitary Adenomas: A Potential Mechanism for Tumorigenesis. Pathol Anat Cell Biol Resid Posters [Internet]. 2014 Jul 1; Available from: http://jdc.jefferson.edu/pacbresidentposters/6

For correspondance: Mohammed Barigou, service d'endocrinologie et maladies métaboliques, Hôpital *Larrey* 24 chemin de Pouvourville TSA-30030, 31059 Toulouse cedex 9, France. med_barigou@yahoo.fr.

17 ECE 1204--EP

Clinical Cases Pituitary/Adrenal

Mohammed Barigou

DOI: 10.3252/pso.eu.17ece.2015

Poster presented at: ECE2015 16-20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY

PosterSessionOnline.com