Case Report

GNAS mutated thyroid carcinoma in a patient with Mc Cune Albright syndrome

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ARTICLE INFO
Keywords:
Fibrous dysplasia
Mc Cune Albright syndrome
GNAS mutation
Thyroid
Thyroid carcinoma

ABSTRACT
Mc Cune-Albright syndrome (MAS) is a rare disorder defined by the triad of polyostotic fibrous dysplasia, “café au lait” skin hyperpigmentation and hyperfunctioning endocrinopathies, such as precocious puberty. MAS is caused by an activating post zygotic somatic mutation of GNAS gene, coding for the alpha-subunit of the stimulatory G protein (Gsalpha). In endocrine tissues, this mutation results in overproduction of hormones and endocrine cell hyperfunction and proliferation.

Whereas the association of hyperthyroidism and thyroid adenomas is well known in MAS, the relationship with thyroid carcinoma has rarely been observed.

We report the occurrence of a thyroid carcinoma in an 18-years old woman with MAS, revealed by subclinical hyperthyroidism detected during her systematic annual follow-up. Ultrasound and thyroid scintigraphy revealed the presence of a nodule in the right lobe. Pathology on hemithyroidectomy revealed an unexpected thyroid follicular carcinoma. Neoplastic thyroid cells harbored the GNAS R201C activating mutation. This observation suggests that MAS may predispose patients to thyroid carcinomas and supports the importance of thyroid assessment by physical examination, hormonal blood test and ultrasound, in the follow-up of patients with MAS. Because ultrasound diagnostic is challenging in MAS, needle puncture of palpable nodules should be advised.

1. Introduction

Mc Cune Albright Syndrome (MAS) is a rare disorder defined by the classical triad of polyostotic fibrous dysplasia (FD), “café-au-lait” skin hyperpigmentation and hyperfunctioning endocrinopathies, such as precocious puberty.

MAS is caused by an activating post zygotic somatic mutation of GNAS gene, coding for the alpha-subunit of the stimulatory G protein (Gsalpha), involved in the cAMP cascade, referred to as a gsp mutation (Weinstein et al., 1991). This mutation leads to elevated levels of intracellular cAMP and activation of downstream-dependent pathways. In endocrine tissues, this mutation results in overproduction of hormones and endocrine cell hyperfunction and proliferation.

MAS is associated with hyperfunction of multiple endocrine tissues, including excess of growth hormone (GH) secretion (Cremonini et al., 1992), hyperthyroidism (Feuillan et al., 1990; Congedo and Celi, 2007; Tessaris et al., 2012; Sallum et al., 2008; Mastorakos et al., 1997) or Cushing’s syndrome (Brown et al., 2010).

Whereas the association of hyperthyroidism or thyroid adenomas (Feuillan et al., 1990; Congedo and Celi, 2007; Tessaris et al., 2012; Sallum et al., 2008; Mastorakos et al., 1997) is well known in MAS, the relationship with thyroid carcinoma has rarely been observed (Collins et al., 2003; Collins et al., 2012; Yang et al., 1999).

We report a new case of GNAS mutated thyroid carcinoma in a patient with MAS.

2. Case report

A 18 years old woman with known MAS presented with subclinical hyperthyroidism during her annual follow-up work up.

Her MAS was diagnosed at age 6 because of abnormal bleeding in relation with precocious puberty. She also had skin “café au lait” spots, polyostotic FD, renal phosphate wasting and growth hormone excess.

At age 18, her systematic follow up measurement showed subclinical hyperthyroidism with suppressed serum TSH, less than 0.01 mUI/ml (normal 0.4–3.1), elevated T3 level at 5.2 pmol/L (normal...
Activating Gs mutations were identified in 38% of autonomously functioning thyroid nodules (Parvanescu et al., 2014; Gaujoux et al., 2019) leading to the term “gonadotropin-releasing hormone” (Gh) excess that has been observed in case of tumors. Indeed, women with polyostotic fibrous dysplasia and/or MAS have an increased risk of breast cancer (Collins et al., 2012; Scanlon et al., 2012; Escalante et al., 2011), thyroid adenomas and carcinomas (Yoshimoto et al., 1993; Riminucci et al., 1994). In a cohort of women with fibrous dysplasia, 2/3 of the patients with MAS had involvement of thyroid, when assessed by thyroid ultrasound (US) (Collins et al., 2012).

Activating GNAS mutation in thyroid tissue results in activation of the TSH/G protein/cAMP pathway which is leading to hyperplasia and thyroid hormone production and increased conversion from T4 to T3 (Combest and Russell, 1983; Celi et al., 2008).

However, association of MAS with thyroid malignancies is rare. So far, two cases of thyroid cancer have been described in MAS patients (1.3%) from the NIH cohort (Collins et al., 2012): one case of papillary thyroid cancer in a 14 year old girl and another case of clear cells thyroid carcinoma in a 42 year old woman. In both instances, the Gs mutation was found in the neoplastic tissue. Interestingly, the Gs mutation was not found in adjacent normal tissue. This data supports the oncogenic role of GNAS mutation on endocrine tissue (Collins et al., 2003).

Another case of lipid-rich follicular carcinoma of the thyroid was reported by Yang GC et al., in a 41 year old woman with MAS (Yang et al., 1999).

Incidence of thyroid carcinomas is low, and MAS is also a rare disease. Therefore, in this observation, it is unlikely that the presence of GNAS mutated thyroid carcinomas and MAS was incidental.

Malignancies can involve other endocrine tissues of patients with MAS.

Indeed, women with polyostotic fibrous dysplasia and/or MAS have an increased risk of breast cancer (Collins et al., 2012; Scanlon et al., 1980; Tanabe et al., 1998; Majoor et al., 2018). In a cohort of women with FD from Netherlands and United States (Majoor et al., 2018), breast cancer risk was 3.9 fold increased (95% CI 1.2–8.2) compared with the general population. Risk of breast cancer was increased at a...
younger age, especially in polyostotic FD and thoracic FD lesions. GNAS mutations have also been identified in pathologic specimens of breast tumors in 4 of 9 patients with fibrous dysplasia (44%) compared with less than 1% reported incidence of GNAS positive breast cancer in the general population. Thus, authors recommended screening for breast cancer in women with FD, at a younger age than women in the general population.

In the same way, MAS is associated with GH excess and pituitary adenomas (Akintoye et al., 2002) and GNAS mutations have been identified in human pituitary tumors in non-MAS patients (Landis et al., 1989; Yoshimoto et al., 1993; Lyons et al., 1990). Thus, a pituitary MRI is indicated in case of abnormal hormonal blood tests (IGF1, GH, prolactin) (Javad et al., 2019).

Rare cases of testicular and ovarian malignancies were described in MAS: one patient with testicular cancer (both embryonal carcinoma and a seminoma) was reported by the NIH (Boyce et al., 2012). One case of ovarian virilizing sclerosing-stromal tumor and one case of ovarian epithelial tumor harboring a GNAS mutation were reported (Boussaïd et al., 2013; Chevalier et al., 2015).

The putative pathogenic effect of GNAS in these tumors is supported by the identification of the R201C mutation in ovarian and testicular Leydig cell tumors, in non-MAS patients (Fragosso et al., 1998).

Gastrointestinal malignancies with hepatobiliary and choledochal cysts and pancreatic neoplasms (intraductal papillary mucinous neoplasms - IPMNs) have also been reported in FD (Parvanescu et al., 2014; Gaujoux et al., 2014; Gaujoux et al., 2019). IPMNs occur in up to 50% in patients with MAS (Robinson et al., 2018) whereas pancreatic adenocarcinoma appears to be a rare development in this population, with only 2 reported cases. In these two cases of IPMNs related colloid pancreatic adenocarcinoma in MAS patients, genetic analysis revealed GNAS mutation of the tumor (Parvanescu et al., 2014; Gaujoux et al., 2019).

Out of the context of MAS/FD, somatic activating GNAs mutations have also been reported in digestive sporadic tumors, such as hepatocellular adenoma, hepatocellular carcinoma, cholangiocarcinoma and in up to 70% of pancreatic IPMNs (Nault et al., 2012; Wu et al., 2011; Kanda et al., 2013; Furukawa et al., 2011).

These elements support, on the one hand, the involvement of GNAS mutation in tumorigenesis of hepatobiliary and pancreatic tissue and, on the other hand, the association between MAS and pancreatic neoplasms (IPMNs).

In total, GNAS mutation can affect any tissue and be responsible for malignancy in these.

MAS patients with endocrinopathies should be enrolled in a specific neoplastic screening program. The first step of endocrine malignancies screening is the physical examination (with thyroid, breast, abdomen and testicular palpation) and the biochemistry (with at least, GH, IGF1, prolactin, TSH, T3 and T4). Then, specific imaging exams should be performed, depending on clinical and biological findings, and according to the endocrine organ involved: for instance, pituitary assessment should be completed with an MRI in case of GH excess at biochemistry, and all male with MAS should have baseline testicular ultrasounds (Javad et al., 2019).

Concerning thyroid, according with recommendations, all patients should have an ultrasound exam, in order to characterize subclinical involvement consistent with MAS (Javad et al., 2019). Because of the increased risk of thyroid cancer and diagnostic difficulties encountered with ultrasound in patients with MAS (diffusely abnormal thyroid gland making difficult the identification of malignant changes) (Collins et al., 2012), we believe that, in case of palpable nodule, needle puncture should be advised. Indeed, in this observation, histology revealed thyroid carcinoma whereas ultrasound data was reassuring, with a low risk of malignancy (2-4%) according to TIRADS classification.

Currently, no specific screening is recommended for digestive tumor including IPMNs, but we believe that the most severe cases of MAS and FD (e.g., polyostotic FD, GH excess) should have baseline hepatopancreatoobiliy MRI, as suggests by Parvanescu and al (Parvanescu et al., 2014). Finally, colon cancer screening may be performed in case of excess GH (Katznelson et al., 2014).

4. Conclusion

We report the fourth case of thyroid carcinoma GNAs mutated associated with a Mc Cune Albright Syndrome. Outside the context of FD/ MAS, a GNAS mutation in thyroid carcinoma has been demonstrated in molecular studies, suggesting that MAS may predispose patients to thyroid carcinomas.

Physicians should keep in mind that the risk of thyroid cancer is higher, but the ultrasound diagnostic is challenging in MAS, guiding to needle puncture of palpable nodules.

Consent

The patient has provided consent for publication of this case report.

Declaration of competing interest

All authors state that they have no conflicts of interest.

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