The physiopathology of endocrine impairments is unknown. No circulating antibodies against hormones or hormone receptors seem to be present [2,8]. No characteristic findings are seen in endocrine organ studies at autopsy [16]. It could be hypothesized that overexpression of VEGF might affect several of the endocrine axes because of a disruption of the local balance of angiogenic factors that appear to be important in the regulation of hormone secretion in many endocrine glands. Because dopamine agonists disrupt VEGF signalling, these agents might have a role in the treatment of the endocrine manifestations of POEMS syndrome [17].

In conclusion, prospective studies with systematic and exhaustive endocrine evaluation of patients with POEMS syndrome would be interesting, but remain of limited feasibility in this context of a very rare and severe paraneoplastic syndrome, in which prognosis can be poor due to the other pathologies.

Disclosure of interest

The authors declare that they have no competing interest.

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Hibernoma and multiple endocrine neoplasia type 1 syndrome: A non-fortuitous association? A case report and literature review

Hibernome et néoplasie endocrinienne multiple de type 1 : une association non fortuite ? Un cas clinique et revue de la littérature

Keywords: Multiple endocrine neoplasia type 1 (MEN1); Hibernoma; Endocrine tumors; FDG PET-CT; *MEN1*; *AIP*; Lipoma

Mots clés : Néoplasie endocrinienne multiple de type 1 (NEM1) ; Hibernome ; Tumeurs endocrines ; 18-FDG PET-Scan ; *MEN1* ; *AIP* ; Lipome

1. Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant tumor syndrome arising from inherited mutation of the *MEN1* gene, a tumor suppressor gene, that is located on chromosome 11 (11q13) [1]. This syndrome is characterized by combinated tumours of the parathyroid glands, pancreatic islet cells, the anterior pituitary and adrenal glands. MEN1 is also associated with cutaneous tumors (angiofibroma, collagenoma), adipose tissue tumor (lipoma) and muscle tumor [1–3].

Hibernoma, a rare benign fatty tumor whose properties are similar to the vestiges of fetal brown adipose tissue (BAT) [4], is exceptionally described in patients affected with MEN1 [5–7].

We report here a case of association between MEN1 and hibernoma.

2. Case presentation

A 65-year-old woman (BMI 31.3 kg/m^2) was followed for 20 years for a familial MEN1 syndrome (nonsense mutation on the exon 2: c.292C>T) associating hyperparathyroidism revealed by renal lithiasis (treated by four-gland parathyroidectomy in 1992 and 1999, with reimplantation of superior parathyroid glands on a forearm and a third surgery for cervical recurrence in 2010); islet cell tumors and duodenal gastrinomas (treated by total duodenopancreatectomy in 2007; 25 islet lesions, 4 duodenal gastrinomas, one lymph node metastasis), 8 mm benign non-secretory adrenal adenoma (treated by left adrenalectomy in 2007), a prolactin-producing pituitary microadenoma (treated by dopaminergic agonist since 1996) and many subcutaneous lipomas.

In a context of pulmonary micronodules, a 18F-FDG PET/CT was performed in 2012 and found fortuitously a right hypermetabolic retro-trochanteric "tumor-like" lesion of 45 × 16 × 53 mm, site of abnormally intense FDG hyperfixation (Fig. 1A).

The well-defined character in MRI, the absence of a mass effect on the adjacent muscle structures and the persistence of a fatty interface between the tumor and the surrounding muscles were consistent with the diagnosis of hibernoma (Fig. 1B).

A CT-guided fine needle biopsy was performed, and histological study confirmed the diagnosis of a hibernoma (Fig. 1C).

The genetic analysis on the biopsy with the technique of MLPA (Multiplex Ligation-Dependent Probe Amplification) suggested the presence of a partial gene deletion of *AIP* and a deletion involving a portion of the *MEN1* gene. Analysis of targeted sequencing did not find the familial mutation of the gene *MEN1* (i.e. there seemed to be a loss of the allele with familial mutation).

In this case there was no indication for surgical hibernoma removal, because our patient had neither functional sign nor compression sign in the imaging. Two years after hibernoma size was stable, but she was treated for a colon adenocarcinoma (pT3N1M0), non-related to MEN1 syndrome. She is currently followed for a right thigh benign at the biopsy lipoma that had grown up (measuring 34 × 59 × 74 mm).

3. Discussion

Hibernomas are rare slow-growing benign tumors with morphological features highly similar to brown adipose tissue. Brown adipose tissue enables energy from oxidized lipids to dissipate as heat via uncoupling protein 1 (UCP1), a mitochondrial proton transporter that uncouples electron transport from ATP production [8]. Thus, these cells have a major role in thermogenesis. These cells are abundant in newborns, and their abundance decrease with age. Brown adipose tissue and hibernoma have a typical yellow to brown appearance because of their rich vascularization [9]. The most common sites of hibernomas are shoulder, neck, chest wall, thighs, abdomen, and retroperitoneum [4].

Hibernomas are often associated with rearrangements of chromosome bands 11q13 [10]. The two main differential diagnosis are liposarcoma (malign tumor) and lipoma (benign fatty lesion), and biopsy is usually performed to exclude the diagnosis of liposarcoma.

MEN1 is an inherited autosomal dominant predisposition (usually germline mutations of *MEN1* tumor suppressor gene (located in chromosome 11q13) that are associated with subsequent deletion of the corresponding wild-type allele) to endocrine tumors, including parathyroids, endocrine pancreas, pituitary, adrenal glands, and the diffuse neuroendocrine tissues deriving from foregut; non-endocrine tumors have been observed in MEN1 patients, including ependymoma, meningioma, cutaneous angiofibroma, melanoma, collagenoma, and adipose tissue tumor (lipoma). But hibernoma is not currently classified as a non-endocrine tumor related to MEN1.

Only three observations describing an association between hibernoma and MEN1 have already been published (Table 1).

The first case was a 56-year-old man with a buttock hibernoma [5], the second a 43-year-old man with a right thigh hibernoma [6] and the third a 40-year-old woman with hibernoma on left gluteal region [7]. The three patients were affected with MEN1 syndrome. Thus our case is the fourth described case.

Taking into consideration the four cases, two patients had de novo MEN1 syndrome, whereas usually only 10% of patients with MEN1 have *de novo* mutations [1]. Hibernoma might be associated with non-familial form of MEN1 because these patients could have developed other cytogenetic rearrangements in chromosome 11.

18F-FDG PET/CT revealed fortuitously the hibernoma in two cases. This imaging is very sensible to detect hibernomas, taking advantage of the hypermetabolic nature of these fatty lesions. Characteristics of hibernomas in multimodal imaging were discussed in a recent paper [11].

Three patients had severe lesions or aggressive forms of MEN1 (liver metastases of pancreatic islet cell tumors for the first case, invasive macroprolactinoma for the second case, more than four different tumors and malign gastrinomas in our case), suggesting that hibernoma could be a marker of MEN1 aggressiveness.

Regarding experimental data on hibernomas, their association with MEN1 could be not-fortuitous. Indeed, Nord et al. (2010) have performed genetic analysis in 15 hibernomas. They have shown that deletions in 11q13 were detected in all but one of the 15 cases, and these deletions in 11q13 primarily clustered around the regions covering *MEN1* and *AIP* (*aryl hydrocarbon receptor interacting protein*, a gene involved in 15 to 25 percent of cases of familial isolated pituitary adenoma [12]). Moreover, losses of *MEN1* and *AIP* were detected in 10 and 6 cases, respectively. They have concluded that deletions of tumor suppressor genes *MEN1* and *AIP* (these two genes are situated in 11q13 3 Mb apart) are essential for the pathogenesis of hibernomas [13]. So a loss-of-function in *MEN1* gene in a context of MEN1 syndrome, associated with other cytogenetic rearrangements and deletions in 11q13, including deletions around *AIP* gene, could favor development of hibernomas. In our case, there was a partial gene deletion of *AIP* in the tumor cells (biopsy of the hibernoma) and a deletion involving a portion of the *MEN1* gene. But we