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LETTER TO THE EDITOR

Multiple sclerosis and oncocytic thyroid carcinoma: fortuitous or drug-related association?

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To the Editor,

Sir,

Autoimmune thyroid dysfunction, treatment-related or not, is reported in patients with multiple sclerosis (MS) [1]. We would like to point out another type of thyroid pathology, tumoral, in MS patients, however very rarely encountered. We had recently studied a case of thyroid carcinoma, peculiar by the predominant oncocyte-type component associated to MS.

The patient (man, 28 years) presented with hair loss, diarrhea, thermophobia, tremor, and tachycardia. The medical history revealed allergy (pollen, prawn), and bilateral moderate loss of vision (at the age of 12 years when in North Africa) with probable intermediar uveitis and optic neuritis. Precise data on initial work-up (brain magnetic resonance imaging (MRI), cerebrospinal fluid analysis (CSF), autoimmunity tests, visual evoked potentials) were not available. These complaints may have been a first event of MS. The local team retained a diagnosis of Behcet disease and the patient was treated by oral steroids during 5 years without any relapse.

Sixteen years after the first neurological event, a right iso- and hypoechogen solid, well-limited nodule (2.5 cm, TIRADS 4B) was detected on ultrasound examination. The right thyroid lobe was resected. Microscopy revealed an oncocytic carcinoma with papillary thyroid carcinoma nuclei and vesicular architecture (Fig. 1). The non-nodular thyroid showed lymphocytic foci (some perivascular), perivesicular fibrosis, intrathyroid nerves, and microgranuloma. Tumor cells expressed on immunohistochemistry heterogeneously Bcl2 as well as CD25 and CD52 in sparse nuclei. Most intra- and extratumor lymphocytes expressed CD52, CD25 being expressed in rare lymphocytes. The left lobe was resected 3.5 months afterwards. Radioactive iodide treatment was given followed by levothyrox. At 2.5 months after the first thyroid resection, the patient presented a second neurolgical event, a myelitis with paresia of the right lower limb and bladder dysfunction. Spinal cord MRI showed several cervical and thoracic intra-medullar T2 lesions with one T6 enhanced lesion. Brain MRI revealed multiple infra- and supratentorial T2 lesions suggestive of MS, with two enhanced lesions, fulfilling Barkof criteria. Exhaustive work-up including for sarcoidosis, neuromyelitis optica, and Behçet disease was negative. Cerebrospinal fluid analysis revealed oligoclonal bands: the criteria of MS were fulfilled. Interferon beta 1a was introduced for 2 years then switched to dimethylfumarate because of inefficacy.

Here, we report a case of oncocytic thyroid carcinoma in a case of long-term corticoid treatment. The diagnosis of associated MS was made 2 months after the thyroid resection. The pathogenesis of the oncocyte-morphotype of tumor cells might be explained rather by the hypothesis of MS-related mitochondrial abnormalities such as an enhanced number and activity, previously reported in axons and astrocytes [2]. An impact of the corticoid treatment is less probable given the biphasic inverted "U" effects in neurons with potentiated mitochondrial dynamic after low levels and after long term and high dose of glucocorticoids downregulated mitochondrial glucocorticoid receptor, Bcl2, and function [3]. Of interest would be also the sparse CD25/alpha subunit of interleukin-2 receptor expression in tumor cells. Thyroid dysfunction of

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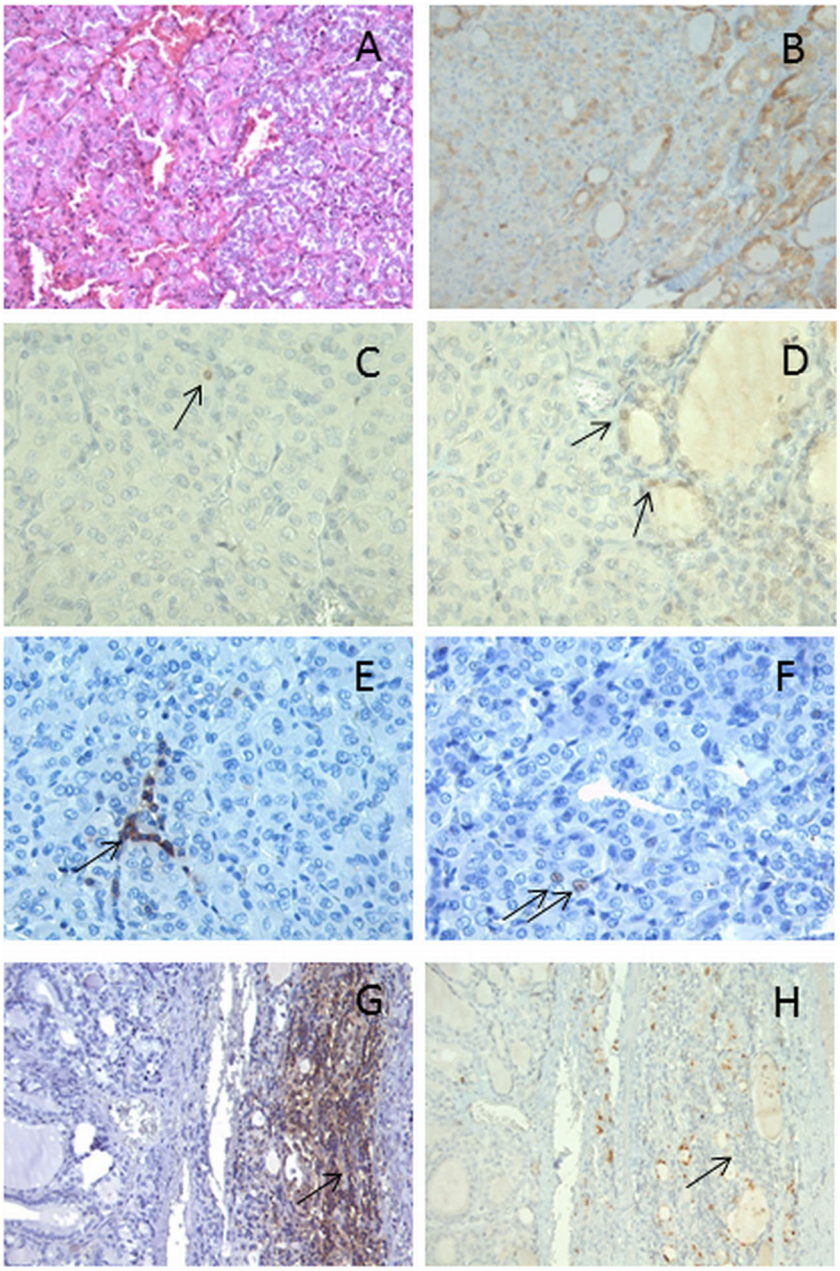

Fig. 1 The papillary thyroid carcinoma was composed of oncocytic cells showing nuclei with ground glass appearance (**a** hematoxylin and eosin stain). Bcl2 was expressed heterogeneously (**b**). CD25 was almost not expressed by tumor cells (**c**, arrow), but expressed by rare intratumor lymphocytes (**d**, arrow). CD52 was expressed in foci of intratumor lymphocytes and in tumor nuclei (**e**, arrow for positive lymphocytic focus; **f**, arrows for positive tumor nuclei). To note would be that CD52-positive lymphocytes outnumbered those CD25 positive in the peritumoral lymphocytic focus present on the serial immunohistochemistry slides (**g** and **h**, arrow)

hypothyroidia or autoimmune type is reported in patients with CD25 mutation/deficiency [4]. Whether the sparse expression of CD25 in tumor cells may also interfere with malignancy remains to be investigated. In addition, our finding of sparse CD25- and more numerous CD52-positive intratumor lymphocytes raises the question of the efficiency of daclizumab or alatuzumab treatments and might give insights for the pathogenesis of treatment-related thyroid dysimmunity. To note would be the expression of CD52 in tumor nuclei. Although normal epithelial tissues such as the tonsil and salivary glands are reported to express the CAMPATH-1M antibody, the relevance of this expression pattern, absent in normal thyroid nuclei, remains to be elucidated [5].

In conclusion, oncocytic thyroid carcinoma may occur in MS. The long corticoid treatment and/or MS-related mitochondrial abnormalities may be incriminated in the pathogenesis of the oncocytic cell morphotype. CD25 and CD52 expression study may give insights for thyroid carcinoma pathogenesis and treatment.

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Compliance with ethical standards

Ethical statement The statements noted on the Internet page of the journal (Instructions for Authors) are fullfilled. Enclosed is the pdf of the Internet page.

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