

Multiple sclerosis, human herpesvirus 4 and thyroid collision tumor: A case report

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Received May 29, 2020; Accepted June 29, 2020

DOI: 10.3892/etm.2020.8975

Abstract. The role of interferon β -1b (IFN β -1b), used for multiple sclerosis (MS) therapy, in cancer occurrence is uncertain. There is evidence supporting the role of human herpesvirus 4 [Epstein-Barr virus (EBV)] in thyroid cancer and MS. Simultaneous occurrence of papillary and medullary carcinomas is rare, and its association with MS in a young woman raises questions. A 46-year-old female patient was diagnosed with relapsing-remitting multiple sclerosis in 2008. In 2018, cervical MRI detected a thyroid nodule with right cervical adenopathy. Her thyroid function was normal, but increased calcitonin levels were found (70.53 pg/ml; normal value: <9.82 pg/ml). EBV serology tested positive. Paraclinical studies ruled out multiple endocrine neoplasia syndrome. Whole thyroid resection with whole cervical lymph node dissection was performed. To our knowledge, this is the first case that describes an association between MS and thyroid collision tumors. Histological examination ascertained both papillary and medullary thyroid cancer. After surgery, the calcitonin level normalized, and the patient received a therapeutic dose of iodine-131. IFN β -1b therapy was discontinued. The coexistence of thyroid cancers in MS patients could be explained by immune-mediated inflammation. Although EBV

is not the only agent responsible for the development of MS or thyroid cancers, it could be considered a contributory factor in our case. Further research on EBV involvement in the occurrence of simultaneous immune pathologies in various organs is needed to confirm these data.

Introduction

Developing from the neural crest, both the brain and the thyroid can be affected by immunological imbalances. Possible associations of cancer with multiple sclerosis and immunomodulatory or immunosuppressant drugs have been investigated. The successive use of two or more disease-modifying therapies for MS patients can increase the risk of neoplasia (1). The results are contradictory regarding this topic, ranging between an increased risk of respiratory cancer, urinary system neoplasia, and nervous system cancer for MS patients and a lower risk of cancer in the MS population (2-5). One study found a higher incidence of thyroid cancer in MS cohort, but it did not specify the type of thyroid neoplasm implicated (1).

Recent studies have revealed that long-term immunosuppressive treatment for MS increases the risk of cancer (6,7). Thyroid neoplasia is the most frequent endocrine cancer, accounting for ~2.1% of all malignancies (8). Differentiated thyroid cancer, including papillary and follicular types, evolving from thyroglobulin-secreting follicular cells, represents ~80% of all thyroid neoplasia cases. Medullary carcinoma, which derives from calcitonin-producing parafollicular C cells, is relatively rare, accounting for 5-10% (9). However, very rare combinations of two thyroid malignancies in the same patient have also been observed. Such cases are known as collision tumors, a rare entity described in the literature as the coexistence of at least two distinct tumors with different genetic origins and histologically distinct morphologies in the same organ and with no transition area between them. Such tumors have been described in the colon, lungs, ovaries, skin, and thyroid gland, with increasing

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Key words: thyroid collision tumors, papillary thyroid cancer, medullary thyroid carcinoma, multiple sclerosis, interferon β -1b, disease-modifying therapy, thyroglobulin, immunohistochemistry, calcitonin, human herpesvirus 4

incidence. Regarding the thyroid gland, the most frequent collision is that of papillary and medullary carcinomas (9). The role of the Epstein-Barr virus (EBV) is often discussed in relation to both MS and thyroid cancers, with a possible association between the two. Collision tumors must be considered more aggressive and posing a greater risk of recurrence compared with independent tumors. Therefore, monitoring cases is more complicated, as the evolution and risks of each tumor involved must be taken into account.

Case report

A 46-year-old female patient was admitted to our clinic in 2018. Her personal medical history included arterial hypertension with preeclampsia, with a first neurological episode of abdominal and crural paresthesia in 2003, when she was 31 years old, which spontaneously remitted within a month. Upon relapse in 2008 with the same symptoms, after a magnetic resonance imaging (MRI) examination, she was diagnosed with recurrent-remitting multiple sclerosis, with an Expanded Disability Status Scale (EDSS) score of 1. Interferon β -1b (IFN β -1b) treatment was initiated at doses of 250 mg (8.0 million IU) subcutaneously every other day. Her family medical history included breast cancer (maternal grandmother) and diabetes mellitus type 2 (father). The course of disease was good after 10 years of treatment, with no evidence of disease activity (NEDA 2): clinical activity, disability progression. In 2018, she was admitted for cervical pain, and cervical MRI examination showed a gadolinium enhancement of the right thyroid lobe. In October 2018, the patient was referred to the Endocrinology Unit for evaluation. No family history of thyroid cancer or multiple endocrine neoplasia (MEN) was reported. Her physical examination was normal. Moderately high serum calcitonin values (70.53 pg/ml; normal value: <9.82 pg/ml) were detected. The patient had normal thyroid function (thyroid-stimulating hormone [TSH]): 1.65 μ IU/ml; normal range: 0.5-4.5 μ IU/ml) and no alteration of calcium metabolism. As her serum parathormone, fractionated plasma, and 24-h urinary total metanephrines were normal, MEN syndrome was excluded. Her serum 25 (OH) vitamin D level was 14.7 ng/ml (normal value: >20 ng/ml). Her immunoglobulin G (IgG) antibodies against EB viral capsid antigen were positive >750 U/ml (negative <20 U/ml), while her anti-EBV nuclear antigen antibody IgG value was 476 E/ml (normal value <5), indicating a prior EBV infection. RET and BRAF V600E gene mutations were not detected.

Ultrasound examination revealed two nodules in the right thyroid lobe: one in the middle third of the posterior part, hypoechoic (14.5x16.9x8.7 mm), with irregular margins, showing micro- and macrocalcifications, with chaotic vascularity in the entire nodule in color Doppler evaluation; the other inferior and lateral to it, a hypoechoic mass (11x10.2x7.9 mm) with regular margins and moderately perinodular flow signals.

The dominant nodule was classified as highly suspected for malignancy. Based on her serum calcitonin level, the patient was referred for surgery. Total thyroidectomy with central compartment cervical lymph node dissection was performed in November 2018. Histopathological examination of the resected specimen identified a collision tumor with a combination of papillary carcinoma and medullary microcarcinoma within the right lobe of the thyroid gland. Medullary

thyroid microcarcinoma is a neuroendocrine tumor derived from C cells (formerly called parafollicular cells) of the ultimobranchial body of the neural crest, which secrete calcitonin, usually located at the junction of the upper and middle portions of the thyroid lobes. This tumor can mimic any other thyroid malignancy of microscopic description. Immunohistochemical examination showed that the patient's medullary thyroid microcarcinoma tumor cells stained positive weak-to-moderate for calcitonin and strong positive for generic neuroendocrine markers (i.e., chromogranin), thyroid transcription factor 1, and carcinoembryonic antigen (Fig. 1) (10,11). One-year follow-up after thyroidectomy showed no evidence of recurrent disease (structural or biochemical).

The study was approved by the Ethics Committee of 'Carol Davila' Central Military Emergency University Hospital (Bucharest, Romania) and the patient's informed consent was obtained.

Discussion

Due to the suspected medullary carcinoma, and because of the preoperatively high level of calcitonin, whole thyroidectomy with central lymph node resection was performed (12). As a consequence of total thyroidectomy through throat dissection, hypoparathyroidism, either transitory or permanent (due to inadequate surgical techniques, local hematoma, blood flow disturbances, or direct glandular lesions) may occur. Some authors have recommended autotransplantation of at least two parathyroid glands in such cases (13,14). After surgery, our patient developed laryngeal diplegia, with the left vocal cord immobilized in the paramedian position and the right vocal cord exhibiting a discrete adduction movement with sufficient respiratory space. The laryngeal nerve palsy recovered within a few months.

Neurological monitoring during thyroidectomy reveals useful information regarding the integrity and functionality of the recurrent laryngeal nerves. In this context, two-stage thyroidectomy is useful (15). Another surgical procedure to preserve the recurrent laryngeal nerve is robotic-assisted breast-axillo insufflation thyroidectomy (RABIT), which allows a simultaneous and symmetrical visualization and an easier approach (16). After surgery, our patient's serum calcitonin levels returned to normal levels (<2 pg/ml; normal value: <11.5 pg/ml), which indicated that there was no residual tumor tissue. For the papillary cancer with microscopic invasion into the perithyroidal soft tissue, the patient was administered radioiodine (50 mCi of iodine-131). Thyroid hormone withdrawal was induced six weeks prior to radioablation. At that time, biochemical tests of the patient's thyroid status showed the following values: TSH >47.6 μ IU/ml (normal range, 0.5-4.5), stimulated thyroglobulin 0.5 ng/ml, and anti-thyroglobulin antibodies <1 IU/ml (normal range, 0-4).

One year after surgery and radiotherapy, the patient was well, with hormonal levels within normal ranges and no evidence of local recurrence on ultrasound. No clinical or imaging signs of MS progression were detected, despite the discontinuation of immunomodulatory treatment with IFN β -1b. Simultaneous occurrences of two or more cancers in the thyroid or in multiple organs have been described in immunosuppressed patients, some with autoimmune diseases, previously administered immunosuppressive treatments (17,18).

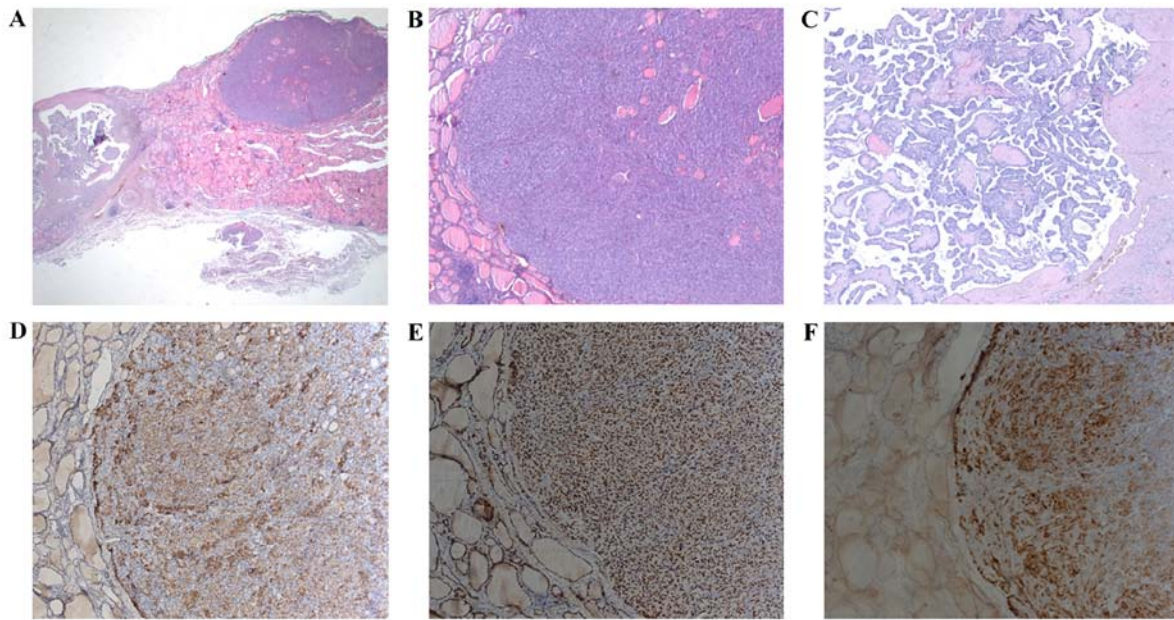


Figure 1. (A) Hematoxylin and eosin stain. Original magnification, x10. First nodule (9x5 mm): medullary thyroid microcarcinoma (right; pT1a N0 Mx). This type is represented in the International Classification of Diseases for Oncology (ICD-O) by the code 8345-3. Second marginal nodule (17 mm): papillary thyroid carcinoma (left; pT1b N0 Mx L1). This type is represented in the International Classification of Diseases for Oncology (ICD-O) by the code 8260-3. (B) Medullary thyroid microcarcinoma. Hematoxylin and eosin stain. Original magnification, x50. This type of tumor, measuring <1 cm in diameter, exhibits a nesting, solid, and trabecular growth pattern. The tumor cells are round, polygonal, and focal spindle-shaped, with round nuclei with coarsely clumped chromatin and eosinophilic-to-amphophilic granular cytoplasm due to secretory granules. (C) papillary thyroid carcinoma. Hematoxylin and eosin stain. Original magnification, x50. This type of infiltrating, partially encapsulated tumor exhibits a papilliferous growth pattern, composed of randomly oriented papillae with a complex arborizing pattern, which are formed by a central fibrovascular stalk covered by a neoplastic epithelial lining, together with the presence of well-formed psammoma bodies or in an early stage of formation. These tumor cells have typical nuclear features and display a characteristic set of abnormalities divided into three major categories: nuclear enlargement and overlapping, circumferential irregularities of the nuclear membrane (garlands), and nuclear pseudoinclusions that represent deep cytoplasmic invaginations into the nucleus. Immunohistochemical staining shows that medullary thyroid microcarcinoma tumor cells stain consistently positive weak-to-moderate for calcitonin and strong positive for generic neuroendocrine markers (i.g., chromogranin), thyroid transcription factor 1 (TTF1), also called thyroid specific enhancer-binding protein, and carcinoembryonic antigen (CEA). (D) Chromogranin. Original magnification, x100. The patient's tumor cells showed strong positivity for chromogranin. (E) TTF1. Original magnification, x100. The patient's tumor cells showed strong positivity for TTF1. (F) CEA. Original magnification, x100. The patient's tumor cells showed strong positivity for CEA.

Exposure to IFN β -1b is not associated with an increased risk of neoplasia (19). It is estimated that infective agents are implicated in 2 million cancers yearly, 10% of which are due to EBV (20). EBV, also known as human herpesvirus 4 (HH4), is found in over 95% of the general population, transmitted through saliva. EBV infects the B lymphocytes, reducing gene expressions from ~100 to just 9 proteins, and has the ability to hide and remain in a latent state for years (21). While the incorporation of viral DNA in that of the host cell is well known, the oncogenesis mechanism has not yet been identified (22). EBV genome examination by polymerase chain reaction detected EBV DNA in 71.9% of a thyroid cancer patient cohort. Other authors reported similar findings (23,24). Another study, however, did not confirm the association between thyroid tumors and the presence of EBV (25). EBV involvement in MS etiopathogenesis has been extensively studied (26). B lymphocytes hosting EBV are involved in triggering aberrant immune responses in multiple sclerosis, associated with genetic predisposition and environmental factors as a background. The EBV involvement in MS etiopathogenesis have been revealed by serological studies and the detection of the virus in patients' brains (27).

However, vitamin D deficiency, confirmed in our case also correlates with thyroid cancers and MS. Meta-analyses have associated an optimum level of 25 (OH) vitamin D with a low risk of thyroid cancer (28,29). Although vitamin D

levels are associated with increased MS, the role of supplement doses should be further investigated (30). Difficulties in supporting differential diagnosis, or in the medical or surgical approach of patients with chronic neoplastic conditions are inherent (31-34), but early detection and intervention increase survival and quality of life.

In conclusion, the coexistence of thyroid cancers in MS patients could be explained by an immune-mediated inflammation involved in both pathologies. Although EBV is not the only agent responsible for the development of MS or thyroid cancers, it could be considered a contributory factor in our case. Simultaneous onset of medullary and papillary thyroid carcinoma is rare. Treatment and follow-up strategies should be individualized according to the aggressiveness of tumors. Further research on EBV involvement in the occurrence of simultaneous immune pathologies in various organs is needed to confirm these data.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AMSi, CAS, LE, AMSo, MCG and FIR were involved in the conception of the study. AMSi, CAS and LE contributed equally to the acquisition of the data and the drafting of the manuscript. AMSo, MCG and FIR contributed equally to the critical revisions of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of 'Carol Davila' Central Military Emergency University Hospital (Bucharest, Romania).

Patient consent for publication

The patient's informed consent was obtained.

Competing interests

The authors declare that they have no competing interests.

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