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A nodule on the scalp as the first sign of extranodal disease in medullary thyroid carcinoma

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Abstract

Medullary carcinoma of the thyroid gland accounts for only 5-10% of thyroid carcinomas. Also, metastases to the skin of malignant tumors are infrequently (2-9% of patients). In the case herein reported in a 64-year-old woman, a metastatic nodule on the scalp was the presenting clinical manifestation of a medullary thyroid carcinoma. A comprehensive review of the literature was conducted for similar cases using PubMed. Only 18 cases of cutaneous metastases of medullary thyroid carcinoma have been previously reported in the literature, but skin lesions were the presenting complaint of the thyroid neoplasm in only three.

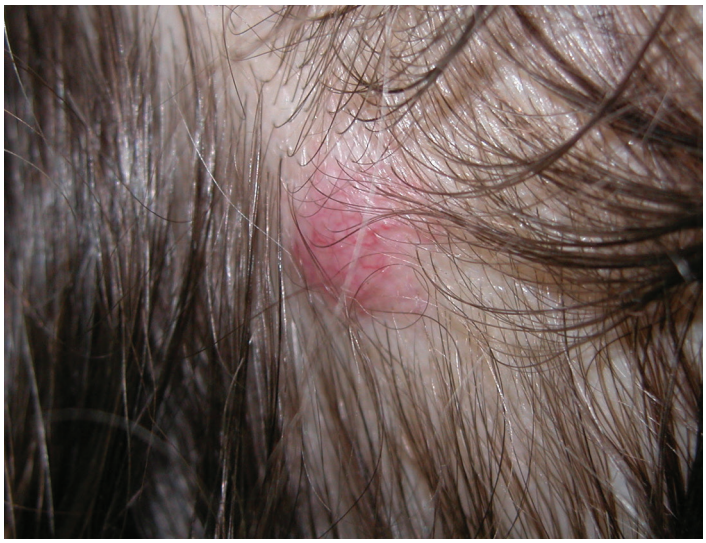

Figure 1. *Erythematous nodular skin metastasis on the frontoparietal area.*

Keywords: skin metastasis, medullary thyroid carcinoma, thyroid neoplasm, scalp

Introduction

Cutaneous metastases of internal malignancies are relatively uncommon, with a reported incidence that varies from 2% to 9% [1, 2]. Most cases occur late in the course of the disease, but cutaneous metastasis may also be the initial presentation of the neoplastic disease. Breast cancer in women and lung cancer in men, followed by cancer of the colon, kidney, ovary, and melanoma are the most frequent primary tumors [3]. Cutaneous metastases from carcinomas of the thyroid gland are a rarity but even more so when they arise from a medullary thyroid carcinoma (MTC). MTC is an aggressive tumor of parafollicular C cells, which readily metastasizes to regional lymph nodes. This tumor is rare and accounts for only 3-5% of thyroid cancers [4].

A limited number of cases of cutaneous metastasis of MTC have been published in the literature [5-14]. We report a patient who developed a single scalp metastasis as the first sign of extranodal involvement of MTC.

Case Synopsis

A 64-year-old woman with no family history of thyroid cancer or other endocrine diseases, presented with a 2-month history of an erythematous scalp nodule, one cm in diameter, in the left frontoparietal region

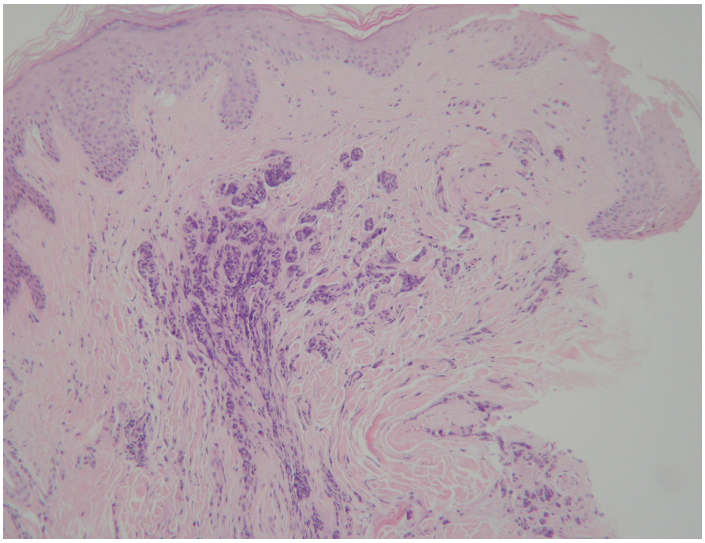

Figure 2. *Indian file infiltration by atypical cells of thyroid carcinoma in the dermis (H&E, 100x).*

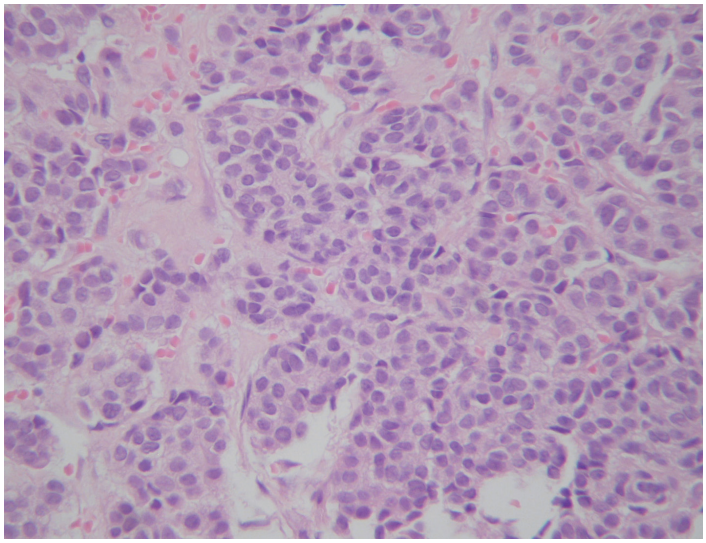

Figure 3. *More detail of metastasis of thyroid carcinoma organized into nests separated by a highly vascular stroma (H&E, 400x).*

(**Figure 1**). The patient noted an accompanying history of bone pain and systemic symptoms, with a weight loss of 10 kg over the past 3 months. The nodule was biopsied and submitted for histopathological examination. Histologically, the nodule was composed of atypical cells that tended to infiltrate as individual rows [Indian file invasive pattern, (**Figure 2**)]. Individual cells were large, round to polygonal, and organized into nests separated by a highly vascular stroma. The cytoplasm was abundant, eosinophilic, and granular. Some mitotic and aberrant multinucleated cells were observed (**Figure 3**). The neoplastic cells stained positively for calcitonin (70% of cells) and carcinoembryonic antigen (CEA) but negatively for thyroglobulin. The findings were consistent with a diagnosis of medullary thyroid carcinoma. During investigation, a thyroid mass (2 x 3 cm in diameter) and enlarged cervical nodes were palpated. Laboratory tests were unrevealing except for a normocytic anemia and increased levels of calcitonin and carcinoembryonic antigen (CEA). Plasma calcitonin levels were 1.77 µg/L (normal value < 0.02 µg/L) and serum levels CEA 3418 µg/L (normal value ≤ 3.4 µg/L). Serum levels of chromogranin A were not measured. RET proto-oncogene germline mutation test was negative. Thoracoabdominal computed tomography (CT) scans and bone scintigraphy studies showed liver and bone metastases. The patient underwent total thyroidectomy and lymphadenectomy. Histologic examination of the surgical specimen confirmed the diagnosis of medullary carcinoma. Micrometastases in six cervical lymph nodes were present. The patient received best supportive care and died one month later.

Case Discussion

Thyroid medullary carcinoma is a well-characterized neuroendocrine tumor arising from calcitonin-secreting C cells and RET gene generally plays a central role on its pathogenesis. Despite its rarity, MTC is one of the best characterized solid tumors in terms of pathological, biochemical, and genetic properties. MTC can be sporadic or part of several familial syndromes. Sporadic cases are developed in individual patients with no family history of MTC and account for around 75% of all MTC. Familial cases are autosomal dominant inherited. Thus, the cases can be traced from the proband among first-degree relatives. Classically familial syndromes include familial-MTC and multiple endocrine neoplasia 2 (MEN2). MEN2 is further divided into MEN2A (that normally is associated with MTC, pheochromocytoma, and hyperparathyroidism) and MEN2B (that includes MTC, pheochromocytoma, Hirschsprung disease, and Marfan-like phenotype among other entities). Also, MTC is included in the list of neuroendocrine tumors causing paraneoplastic syndromes (e.g. Cushing's syndrome) [15, 16]. Understanding MTC biology, clinical manifestations, treatment, and prognosis is based extensively on the discovery of tumor-specific mutations and the abnormal expression of several tyrosine kinase receptors and pathways. In our patient, MEN was excluded by the negative

oncogene RET mutation test and the absence of a familial MTC history. Our patient showed increased calcitonin and CEA levels, and 70% of cells stained for calcitonin. However, serum levels of chromogranin A were not determined.

Cutaneous metastases associated with medullary carcinoma of the thyroid gland have been uncommonly described. Sanii et al. [5] had found 15 reported cases in the English literature up to 2011 [6-12], and added a case in which metastatic lesions to the skin were the earliest sign of the thyroid neoplasm. However, a previous case described by Dahl et al. [1] in 1997 was not included in the review. Recently, two other cases of cutaneous metastases of MTC have been reported, but in none of these patients were skin metastases the initial manifestation of the thyroid tumor [13, 14]. Therefore, adding our patient, a total of 20 cases of metastatic medullary thyroid carcinoma to the skin have been described. Cases identified in autopsy studies were not included [1, 17].

The frequent presentations of cutaneous metastases from MTC were solitary or multiple erythematous-to-violaceous papules in the dermis or subcutaneous tissue. Lesions mostly developed on the chest, scalp, back, neck, supraclavicular area, forearm, and flank. The skin metastases usually present as flesh-colored nodules that are tender; they may be itchy and can be ulcerated. MTC can metastasize to regional lymph nodes, but may also spread hematogenously to affect liver, lungs, bones, and rarely brain and skin. The majority of patients develop cutaneous metastases in the presence of known distant metastases, indicating systemic spread of thyroid cancer. Sanii et al. [5] reported a case in a 79-year-old woman in whom painful skin lesions were the first manifestation of MTC. In two cases described by Alwaheeb et al. [10], skin metastases were also the first manifestation of a previously undetected medullary carcinoma in the thyroid gland. Ghanadan [13] reported a case of asynchronous metastasis of MTC to skin, 4 years after thyroidectomy for MTC. Also, Mannan et al. [14] described a case of a patient with the primary complaint of multiple subcutaneous nodules of the anterior chest wall and left side of the mandible, which were diagnosed as cutaneous metastasis of MCT. This patient had intermittent episodes of flushing and subsequently provided a history of thyroid surgery 5 years back at another center. The cutaneous metastasis of MTC is a sign of dissemination and reflects a very poor prognosis. In our patient, the nodule of the scalp was the first sign of extranodal dissemination of MTC. However, work-up studies showed concomitant liver and bone metastases, and the patient died one month later. Multidisciplinary teams and specialized centers are recommended for the management of MTC patients. In the metastatic setting, those patients with a large volume of disease are candidates to start systemic treatment mainly if they are symptomatic and the tumor has progressed in the last 12-14 months. Wait-and-see strategy should be offered to patients with: disseminated disease with only high levels of calcitonin and no macroscopic structural disease or low burden and absence of progression [18].

In summary, cutaneous metastases of MTC are very rare and may uncommonly present as the first manifestation or clinical sign of extranodal spread of the primary tumor. MTC metastases should be included in the differential diagnosis of erythematous popular cutaneous eruptions and nodules, especially when the lesions are located on the upper part of the body, particularly in the scalp. Characteristic histological features and analysis for neuroendocrine markers are required for a correct diagnosis of MTC.

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