

Short Communication

Mixed medullary and follicular carcinoma of the thyroid – A rare entity

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Mixed medullary–follicular carcinoma is an uncommon tumor of the thyroid. It is characterized by histological and immunohistochemical features of both follicular and parafollicular C cells. We report a case of medullary carcinoma of the thyroid in a 26 year old female, which on light microscopy, showed not only the well known arrangement of cells in sheets and nests, but also unequivocal follicular structures. Precise diagnosis of mixed medullary-follicular carcinoma is essential for accurate treatment and follows.

Key words: Thyroid, mixed medullary-follicular carcinoma.

INTRODUCTION

Medullary thyroid carcinomas (MTCs) comprise 5 to 10% of all thyroid carcinomas. Although a majority of these tumors occur sporadically, about 20% have a familial background (Murray, 1991). MTCs are assumed to evolve from the neural crest or ultimobranchial body-derived C-cells (Le Douarin, 1982; Williams et al., 1989), and are regarded as being closely related to tumors of the disseminated neuroendocrine system. In the late 1970s it was noted that the histological appearance of Medullary Thyroid Carcinoma (MTC) may be "atypical" and that follicular structures can be encountered in these tumors in addition to typical medullary features (Bussolati and Monga, 1979). Subsequently it was shown that in addition to the characteristic calcitonin immunoreactivity in such atypical MTCs, thyroglobulin (Tg) was detectable in the foci having a follicular appearance, and that the same histological and immunohistochemical pattern was also present in their metastatic lesions. Hence it was proposed that these tumors might represent a new entity, which was termed "mixed medullary-follicular carcinoma" (MMFC) (Pfaltz et al., 1983; Hales et al., 1982). In the second edition of *Histological Typing of Thyroid Tumors*, (Hedinger et al., 1988) Hedinger and associates defined MMFC as "tumors which show the morphological features of both a medullary carcinoma with immunoreactivity for

calcitonin and a follicular carcinoma with immunoreactivity for thyroglobulin.

These tumors are rare and less than 40 cases have been described in the literature since the early 1980s (Kostoglou-Athanassiou et al., 2004). Most reported cases have lymph node involvement at the time of diagnosis. In cases having disease progression, distant metastases develop in the lung, liver, mediastinum and bone. They should be distinguished from MTCs with follicles (Harach and Williams, 1983) or papillae (Kakudo et al., 1979) as well as from MTCs with entrapped normal follicles at their infiltrating edges. Here we report a case of neck mass in a 26 year old female, which on light microscopy consisted of both follicular and parafollicular cells.

Case summary

A 26 year old woman presented with a lump in the right side of the neck, increasing in pain and size over several weeks. She did not drink or smoke. Her family history was free of any endocrine or non-endocrine malignant tumors. There was no history of neck or whole body irradiation. The levels of T3, T4 and TSH were within normal limits. Fine-needle aspiration cytology through the nodule in the right lobe of the thyroid suggested a diagnosis of medullary thyroid carcinoma. Her blood calcitonin level was remarkably high (111 µg/µl). Total

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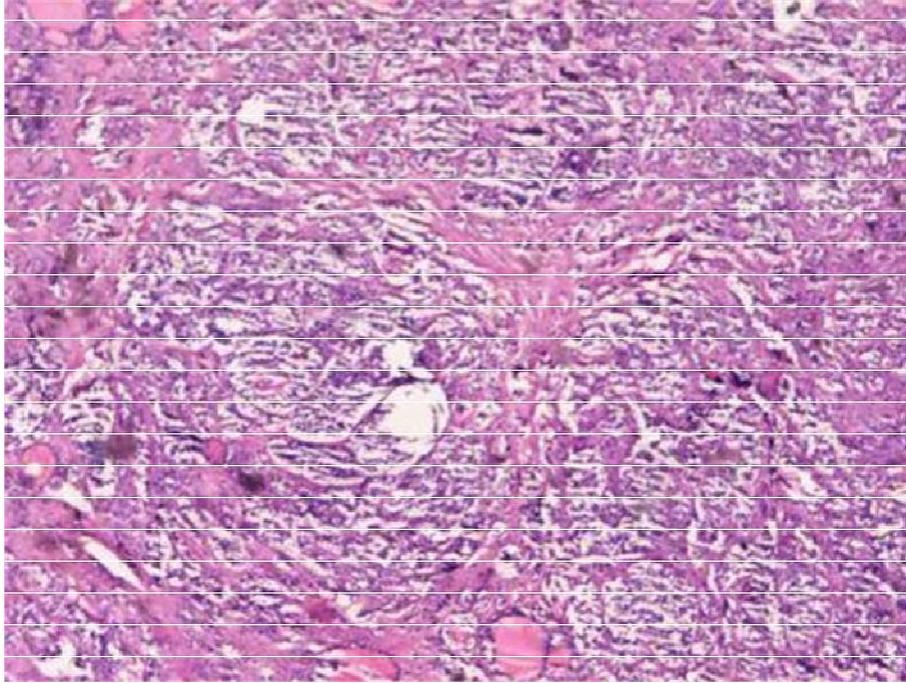


Figure 1. Tumor cells in medullary carcinoma area (Haematoxylin and Eosin X 100).

thyroidectomy was performed initially and she was subsequently given levothyroxine 100 g/d.

Macroscopically, a white colored nodule 1.5 cm in diameter on the right lobe was detected. There were two lymph nodes 1 x 1 and 0.6 x 0.6 cm, respectively, attached to the dissection material.

Microscopically, on cut section of the nodule, a tumor separated by a thin fibrous capsule from the peripheral thyroid tissue was observed. The tumor was centrally hyalinized and there were follicular structures at the periphery. The follicular structures in the tumor contained scanty amount of colloid compared to the follicular structures in the surrounding thyroid tissue. The hyalinized area at the center of the tumor contained islets and trabeculae formed by oval, or spindle cells consistent with medullary carcinoma (Figure 1). Histochemically, there was no evidence of amyloid by using crystal violet. Immunohistochemically, the tumor cells consistent with medullary carcinoma were observed expressing calcitonin (Figure 2). The lymph nodes sampled showed no metastasis.

DISCUSSION

It is known that medullary carcinoma of the thyroid was described by Pfaltz et al. (Pfaltz et al., 1983) in 1959 as a different clinical and pathological entity showing solid, non-follicular pattern. In 1982, Hales et al. (Hales et al., 1982) reported a case of thyroid carcinoma exhibiting

mixed medullary-follicular pattern. Mixed medullary-follicular carcinoma was described as a distinct entity under the malignant epithelial tumor groups of the 1988 World Health Organization (WHO) classification.

The cellular origin of the mixed medullary-follicular carcinoma is not exactly established, yet one of the hypothesis shows that the tumor might arise from the multipotent stem cells and that ultimobranchial rests might have a role. An alternative hypothesis presumes that a common oncogenic stimulus that affects both follicular and parafollicular cells might play a role (Papothi et al., 1997). This tumor is particular seen in middle-aged patients, and a swelling on the neck is generally the initial symptom. Serum calcitonin level is reportedly high in all the cases, as in our case. The size of the tumor might vary between 1 and 5.5 cm is generally unifocal, as observed in our case, while multifocal tumors are particularly associated with MEN type II A.

In most of the cases, lymph node metastasis is detected at the time of diagnosis (Kostoglou-Athanassiou et al., 2004) unlike our case. Foci consistent with medullary carcinoma were observed in our case, and in these foci immunohistochemical findings supporting the medullary carcinoma were detected. As thyroglobulin immunoreactivity was shown in tumor cells forming the follicular structures, mixed medullary-follicular carcinoma diagnosis was facilitated. Because of the limited number of cases and the different regiments of therapies administered to the reported patients, the treatment of mixed medullary-follicular thyroid carcinoma remains

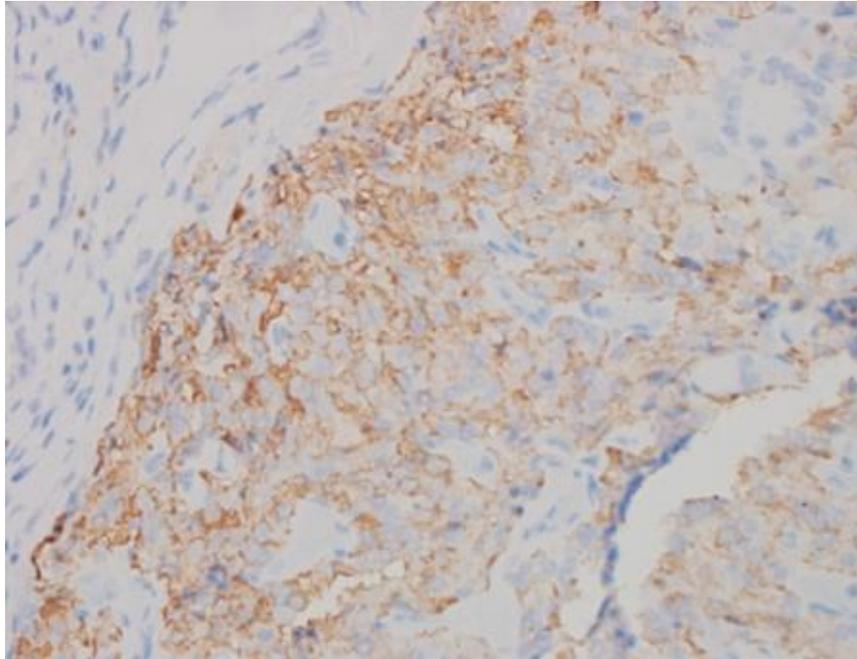


Figure 2. Calcitonin reactivity in medullary carcinoma cells (Calcitonin X 100).

debatable (Volante et al., 1999) . Surgery is accepted as the first-choice for treatment. The role of adjuvant therapies, including radioiodine and chemotherapy remains for further investigation. Our patient had abnormally elevated levels of calcitonin at the time of diagnosis. She was treated initially with surgery (Total Thyroidectomy) and subsequently with levothyroxine 100 g/d.

In the follow up of the patients blood calcitonin and thyroglobulin levels might be helpful. Distant metastasis can be observed frequently in lungs, liver, mediastinum and bones, and the patients might die within 10 years of diagnosis (Kostoglou-Athanassiou et al., 2004). So diagnosis of mixed medullary-follicular carcinoma is essential for appropriate follow-up and treatment.

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