

A Clinical Case Report of Cribriform-Morular Variant of Papillary Thyroid Carcinoma with Neuroendocrine Differentiation and Aggressive Behaviour in a Patient with Familial Adenomatous Polyposis Coli

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Abstract. Cribriform-morular variant of papillary thyroid carcinoma (CMVPTC) is a rare variant of papillary thyroid cancer mostly occurring in young females under the age of 30. CMVPTC is associated with familial adenomatous polyposis coli and has an excellent prognosis with most patients surviving upwards of 20 years. We describe the clinical course of an aggressive variant of CMVPTC in a 42-year-old male with the first known reported features of neuroendocrine differentiation (the unusual histological features are published elsewhere in a separate article (Cameselle Teijeiro, J., et al. *Am. J. Clin. Pathol.*, 131:134-142, 2009). The patient survived just 23 months from diagnosis and we outline our management here including the use of radiolabelled Yttrium 90 therapy.

Keywords. Cribriform-morular variant • Familial adenomatous polyposis • Neuroendocrine differentiation • Papillary thyroid carcinoma

Introduction

Cribriform-morular variant of papillary thyroid carcinoma (CMVPTC) is a rare variant of papillary thyroid cancer that predominantly occurs in young females under the age of 30 and is often associated with familial adenomatous polyposis coli (FAP) and a good prognosis. We describe the clinical course of the first known case in the literature (the unusual histological features of this case having been previously published elsewhere)^[1] of an aggressive variant of CMVPTC with features of neuroendocrine differentiation in a 42-year-old male and the subsequent management strategy.

Case History

Whilst undergoing colectomy for his FAP, a 42-year-old man was found peri-operatively to have a thyroid mass. Fine needle aspiration showed features of a papillary carcinoma. As a result he underwent total thyroidectomy and central compartment clear-

ance. He had a familial history of colon carcinoma that affected his maternal grandfather, his mother, 2 of 5 maternal uncles, and 1 cousin. His mother and his only brother also had osteomas.

The right lobe of the thyroid was almost entirely replaced by a solid, fleshy, haemorrhagic yellowish tumour. The histological diagnosis was that of an angioinvasive cribriform-morular variant of papillary carcinoma showing neuroendocrine differentiation. Approximately 40% of the tumour cells expressed chromogranin and synaptophysin. They were negative for calcitonin and thyroglobulin. Molecular studies showed germline and somatic APC gene mutations as well as RET/PTC rearrangement but no BRAF, nor RAS mutations were found. Seven lymph nodes were resected and all were free of tumour. Inflamed diverticuli were found in the colectomy specimen but no adenomatous polyps were present. The unusual histological features of this case were published in more detail in a separate article by Cames-

elle-Teijeiro, et al.^[1]

Staging thoracic CT scan showed bilateral pulmonary metastases without any clinical symptoms. The patient's serum thyroglobulin was undetectable without thyroglobulin antibodies. Six months following initial diagnosis, he developed multiple brain metastases and right neck nodal metastasis. His brain metastases were treated with palliative whole brain radiotherapy. He was considered for radio-labelled octreotide therapy in view of the presence of neuroendocrine differentiation in the tumour. Octreotide-111Indium scan showed significant uptake in the right neck and lungs. He was treated with 5 GBq of dotatoc-⁹⁰Yttrium.

The patient had a good clinical response with significant reduction in the size of the metastatic mass in the right neck. The duration of his good response however, proved to be short-lived, as a CT scan 4 months post dotatoc therapy showed progressive disease. He underwent a further 5 GBq of dotatoc-⁹⁰Yttrium therapy with significant uptake in the neck lesion but no uptake in the lung and brain metastases. He died 6 months after his second dotatoc-⁹⁰Yttrium therapy, having survived just 23 months from the time of diagnosis.

Discussion

Thyroid carcinoma as an extra-intestinal manifestation of FAP has been well documented. The prevalence is thought to be as high as 12%.^[2] The adenomatous polyposis coli (APC) gene plays an important role in the development of cribriform-morular variant of papillary thyroid carcinoma.^[3] The CMVPTC is a rare variant of thyroid cancer with an estimated prevalence of 0.16% of all papillary thyroid cancers and is usually associated with a good prognosis.^[4]

Both conventional PTC and CMVPTC associated with FAP predominantly occur in females under the age of 30 and are usually multi-focal. CMVPTC tends to behave in a similar manner to conventional papillary thyroid carcinoma; Cameselle-Teijeiro, et al. published seven of nine cases reported to be alive and completely disease free 1-13 years after follow up.^[5] Most patients with FAP associated PTC survive long term with survival rates of up to 77% at 20 years.^[6] In contrast our 42 year old male patient had an aggressive disease course and survived only 23 months.

The unusual features present in this case (i.e. high nuclear atypia, high mitotic activity, high pro-

liferation index, marked angioinvasion, neuroendocrine differentiation, overexpression of cyclin D1 and strong expression of P53) suggested a "less-differentiated" (poorly differentiated) CMVPTC.^[1] These features correlated well with the aggressive course of disease seen in this case.

Most reported cases of CMVPTC usually involve encapsulated or locally advanced tumours without distant spread. The usual treatment of such cases consists of total/near total thyroidectomy with or without radioiodine therapy.

The principal reasons for pursuing dotatoc therapy in this case were the advanced nature of the disease and the neuroendocrine component of the tumour with negative staining for thyroglobulin; radioiodine treatment would likely have been ineffective. The MAURITIUS study^[7] showed evidence of a 56% response rate (either regression or stable disease) following treatment with 1 to 4 doses. There were no episodes of serious adverse events reported.

Most papillary thyroid carcinomas are associated with one of two mutations: RET/PTC rearrangement and BRAF mutations. Accordingly, our patient was considered for Sorafenib which is known to target cell signaling mechanisms involving VEGF and BRAF, and which has been evaluated in phase 2 studies in advanced thyroid cancers.^[8] However, given the absence of BRAF mutation, this therapeutic avenue was not pursued.

Conclusions

We describe additional information about the first case of CMVPTC showing neuroendocrine differentiation in a patient with FAP associated with other striking features including the atypical age, gender and aggressiveness of disease. In spite of our patient's final outcome, based on the increasing knowledge of the molecular pathophysiology of thyroid cancers, clinicians should consider novel therapies as one potential therapeutic option when faced with treating rare tumours of this nature.

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