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Case report

Cribiform-morular variant of papillary thyroid carcinoma and familial adenomatous polyposis: report of a case and literature review

Mario Giuffrida[1], Federica De Giorgi[2], Federico Cozzani[1], Matteo Rossini[1], Elena Bonati[1], Paolo del Rio[1]

[1]General Surgery Unit, Parma University Hospital, Italy
[2]Department of Human Histopathology, Parma University Hospital, Parma, Italy

Abstract. Cribiform-morular thyroid carcinoma is a rare variant of papillary thyroid carcinoma. It is usually related to Familial Adenomatous Polyposis (FAP) but rarely it may be sporadic. This variant of PTC occurs in young females and it is rare in the elderly. We report a case of a 20-year-old female presenting thyroid carcinoma and personal history of FAP. (www.actabiomedica.it)

Key words: familial adenomatous polyposis, papillary thyroid carcinoma, FAP, thyroid

Introduction

Thyroid cancer is the most common endocrine malignancy. The cribriform-morular variant (CMV) is a very rare histological subtype of thyroid carcinoma. This variant of papillary thyroid carcinoma (CMV-PTC) is usually a well-differentiated thyroid tumor and has generally a good behavior. It was first described in 1994 in patients with familial adenomatous polyposis (FAP). Later, sporadic CMV-PTC was also found in patients without polyposis, and it was first described in 1999 (1-3).

Molecular mechanisms involved are mutation of the adenomatous polyposis coli (APC) gene or catenin gene, which promote the development of FAP and extra-colonic associated malignancies (4).

We report a case of a young woman with a rare form of thyroid cancer associated to FAP.

Case Report

A 20-year-old woman presented to our surgical department with personal history of FAP and previous total colectomy. The patient has also a strong family history of FAP: both her father and sister had undergone total colectomy for FAP. At the age of seven the genetic analysis revealed the mutation of APC gene and confirmed the diagnosis of FAP. Colonoscopy revealed multiple polyps throughout the colon that were proven to be tubular lesions with low-grade dysplasia on histological examination. The patient was followed through the years and she underwent laparoscopic total colectomy when she was 17. Histopathological examination confirmed the diagnosis. She had an uneventful recovery and was discharged 7 days after surgery.

During endocrinological follow-up for FAP, physical examination did not reveal any pathological features. Clinically, she was euthyroid with no evidence of upper airway obstruction, hoarseness or dysphagia. Thyroid ultrasound demonstrated a 5 mm hypoechoic nodule in the right thyroid lobe and two hypoechoic nodules of 9 and 13 mm in the left thyroid lobe, without regional lymphadenopathy.

Cytological examination with fine needle aspiration (FNA) showed the presence of atypical epithelial cells, organized in multilayer sheets and big groups,

with large, irregularly shaped and crowded nuclei, some of which presented nuclear grooves: all of these findings were indicative for a malignant thyroid cancer (Category VI, according to the Bethesda 2017 classification system).

In line with the diagnosis, the patient underwent total thyroidectomy MIVAT (Minimally Invasive Video-Assisted Thyroidectomy) with IONM (intraoperative neurophysiologic monitoring). The post-operative period was uneventful. On the second day after surgery, she was discharged.

Macroscopic examination of left thyroid lobe showed two whitish, clean-edged nodules of 1.3x1x1 cm and 0.4x0.3 cm, while right thyroid lobe showed a nodule of 0.4x0.3 cm with similar macroscopic features.

Histopathological evaluation showed well-circumscribed proliferations of cells, growing in a mainly compact structure, with a sometimes-incomplete fibrous capsule. Cells were slightly elongated or cuboidal/cylindric, organized in papillary, trabecular or pseudo-follicular configurations, interspersed cell clusters arranged in squamous islands (morules) and columnar cells, without colloid. The nuclei were elongated, with scattered nucleoli and pseudonuclear inclusion (Fig. 1).

Immunohistochemical staining for beta-catenin showed diffuse nuclear and cytoplasmic staining; Thyroid transcription factor (TTF-1), Estrogenic Receptor (ER) and Progestinic Receptor (PR) were positive in tumor cells but negative in morules, which were positive for CD10. The BRAF-V600E mutation was immunohistochemically absent.

Discussion

CMV-PTC is only 0.1–0.2% of all papillary thyroid cancers and was described for the first time in 1994,

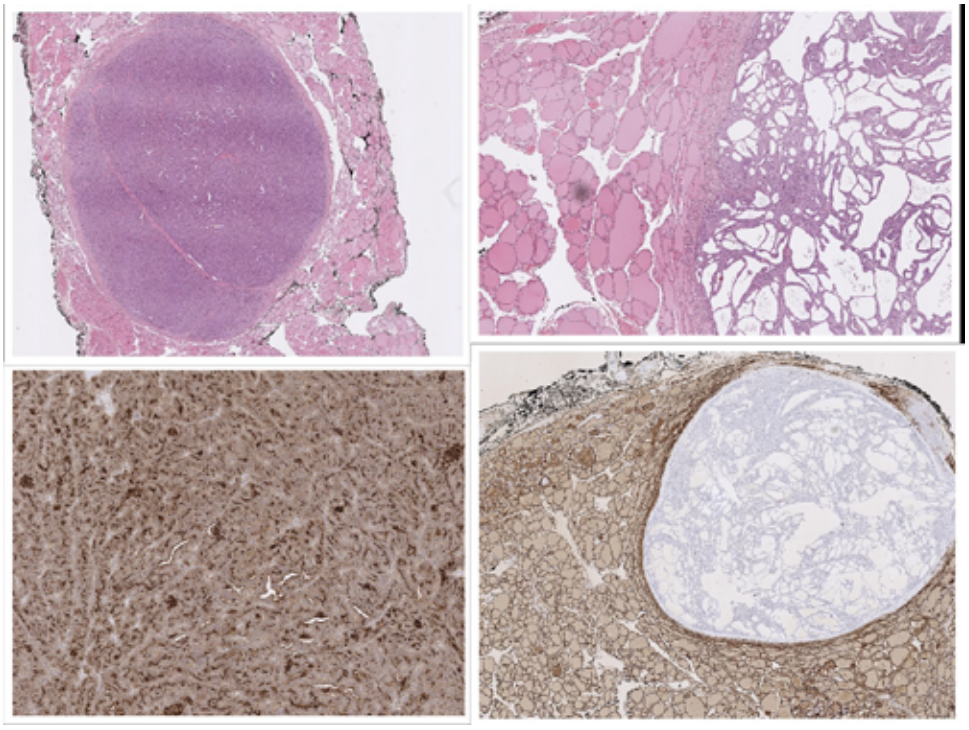

Figure 1. Microscopic examination (Cells were slightly elongated or cuboidal/cylindric, organized in papillary, trabecular or pseudo-follicular configurations, interspersed cell clusters arranged in squamous islands (morules) and columnar cells, without colloid; immunohistochemical staining for beta-catenin showed diffuse nuclear and cytoplasmic staining).

as a particular thyroid carcinoma observed especially in patients with FAP (1-7). Sporadic forms of CMV-PTC without FAP diagnosis were also found (2).

FAP is an autosomal dominant disorder caused by a germline mutation in the APC gene. FAP leads to the development of several hundreds or thousands of colorectal adenomatous polyps that could progress to adenocarcinoma, and it is sometimes associated with numerous extracolonic manifestations: upper gastrointestinal adenomas and carcinomas, desmoid tumors, thyroid cancers, pancreatic cancers, hepatoblastomas, congenital hypertrophy of the retinal pigment epithelium (CHRPE), osseous tumors, brain tumors, epidermoid cysts in the skin, osteomas of the mandible, dental abnormalities, lipomas, or fibromas (8-10).

The presentation of CMV-PTC usually occurs within 10 or more years from initial diagnosis of FAP, but it has been reported that CMV-PTC can precede the diagnosis of FAP. CMV-PTC can be diagnosed 4-12 years before the onset of FAP manifestations (1-11).

The prevalence of thyroid carcinoma in FAP patients varies from 2% up to 12%. The relative and absolute risk of developing thyroid cancer is respectively of 7.6% and 2% (11-13).

FAP-associated papillary thyroid cancers is commonly seen in young females (female-to-male ratio of 17:1), usually less than 30 years of age with a mean age of 27.65 years (14-15).

The CMV-PTC has a very unusual histology, presenting classic papillary and cribriform patterns (16).

Macroscopically FAP-associated CMV-PTCs are encapsulated and more often multifocal lesions, in contrast to sporadic CMV-PTCs, which frequently appear as a solitary nodule (2).

Histological evaluation shows well-circumscribed proliferations of cells growing in a mixture of architectural patterns including papillary configurations, nuclear elongation, soap-bubble nuclei, intracytoplasmic neutrophils, grooves, overlap and intranuclear inclusions with cribriformed fragments, interspersed cell clusters arranged in squamoid islands (morules) and columnar cells (7,17,18).

Immunohistochemically, CMV-PTCs show intra-cytoplasmic and intra-nuclear positivity for beta-catenin and nuclear ER expression, contrary to what happens in conventional papillary thyroid cancer, which shows cell membrane expression for beta-catenin without nuclear ER expression (19).

FAP occurs due to germ line mutation of the APC gene located on chromosome 5q21 (20).

The APC gene, interacting with beta-catenin, encodes a protein complex (APC protein), that works as a tumor suppressor (21). The combination of the APC gene and beta catenin is responsible for abnormal cellular proliferation, that leads to tumorigenesis. An APC germline mutation is usually observed in FAP associated with CMV-PTC, while somatic mutation is observed in sporadic cases of CMV-PTC. In absence of APC mutation, the mutation of beta-catenin gene (CTNNB1) causes aberrant nuclear accumulation of beta-catenin, leading to CMV-PTC (22).

The prognosis of CMV-PTC seems to be better than other variants of papillary thyroid carcinoma with a five-year survival rate of over 90 % and 20-year survival rate of 77% (7,23,24).

Treatment of FAP-associated CMV-PTC is similar to treatment for usual papillary thyroid carcinoma and it consists of total thyroidectomy, followed by radioiodine therapy. Distant metastases are rarely observed in CMV of PTC (25).

Routine cervical ultrasound screening is not recommended in patients with FAP due to its low prevalence, but ultrasound cost-effectiveness could justify routinely screening, as we made in our case. Nevertheless, the diagnosis of a CMV-PTC in any patient without FAP is an indication for colonoscopy and genetic study of the APC gene sequence.

Abbreviations: CMV-PTC: cribiform-morular variant of papillary thyroid carcinoma; FAP: familial adenomatous polyposis; APC: adenomatous polyposis coli gene.

Ethics approval: Not applicable.

Consent for publication: Written informed consent for the publication of the case details was obtained from our patient.

Conflicts of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Correspondence
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Dr Mario Giuffrida,
General Surgery Unit, Parma University Hospital.
Via A. Gramsci 14, 43126 Parma, Italy
Email: mario.giuffrida4@gmail.com