FAMILIAL SYNDROMIC PAPILLARY THYROID CARCINOMA - REPORT OF TWO CASES

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FAMILIAL SYNDROMIC PAPILLARY THYROID CARCINOMA - REPORT OF TWO CASES (Abstract) Aim: to describe two cases of familial papillary thyroid carcinoma. Material and methods: patients were investigated by fine needle biopsy, MRI imaging and tumor biopsy, (first case) and histological examination of colonic and thyroid tumors (first case) and histological examination of thyroid tumor (second case). Results and discussion: case presentation: first case, 68 years old man had a colonic polyposis (attenuated form with only a few polyps) and a thyroid nodule. After hemicolecction for a supposed colonic carcinoma with liver and lung metastases, histological examination revealed no malignant colonic disease. Two month later the diagnosis of invasive thyroid tumor with lymph node metastases was made, but only an open biopsy was done because tumor invasiveness demonstrated on MTI imaging. The biopsy identified a papillary thyroid carcinoma. Case 2: the son of the patient (30 years old) without known diseases was invited to be assessed for thyroid disease. Ultrasound examination discovered a large nodule with microcalcifications. Microscopic examination done after total thyroidectomy revealed a cribriform morular variant of papillary thyroid carcinoma, a variant that is known to be associated with FAP. Radioiodine ablation was made followed by suppressive thyroxine treatment. In the second case adenomatous polyposis was not found yet. In our knowledge these are the first cases of familial thyroid papillary carcinomas in our setting. Familial history allowed an earlier diagnosis and a good management of the disease in the second case. Conclusions: according to the literature and our first experience, screening for thyroid cancer must be done in all patients with FAP and in those with a FAP proband in the family. Keywords: FAMILIAL NONMEDULLARY THYROID CARCINOMA, FAMILIAL ADENOMATOUS POLYPOISIS, CRIBRIFORM, MORULLAR VARIANT, PAPILLARY THYROID CANCER.

Follicular-derived thyroid cancer represents 60-95% of all thyroid malignancies and at least 5% of the patients have familial disease (1). Familial nonmedullary thyroid cancer (FNMT) may be classified into two categories (1, 2, 3, 4): a. Non syndromic familial tumor syndromes with preponderance of FNMT: familial papillary thyroid...
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carcinoma (FPTC) with or without oxyphilia. FPTC associated with renal papillary renal neoplasia, FNMTMC type 1. b. Syndromic familial tumor syndromes in which nonmedullary thyroid carcinoma occurs with a known frequency: familial adenomatous polyposis – FAP and Gardner’s syndrome, PTEN-hamartoma tumor syndrome, Carney’s complex and Werner’s syndrome.

Familial adenomatous polyposis (FAP) and Gardner’s syndrome (a FAP variant) are produced by a loss of function germ line mutation of APC (adenomatous polyposis coli) gene, a tumor suppressor gene located on the chromosome 5q21(2). First mutation of APC gene was described in 1991 and 800 mutations were identified thereafter (5). It is an autosomal dominant disease with an incidence which varies between 1/8300-1/11300-1/37600 which may be responsible for up to 1% of colonic cancers. Classic form develops in the second decade of life and is characterized by occurrence of hundreds or thousands of adenomatous colonic polyps. Attenuated FAP shows fewer polyps, occurs later in life and carries a lower risk of colonic cancer (6). Extracolonic diseases occur in 70% patients with FAP (5).

First case of an association between FAP and thyroid cancer was reported by Crail (quoted by Half 2009(6)). FAP-associated thyroid cancer occurs especially in women, at young age, and has a particular histology (2, 7, 8). Women with FAP have a 160 times higher risk developing thyroid cancer compared with general population (6).

FAP-associated thyroid carcinoma is a syndromic form of FNMTMC and occurs with the following reported incidence: Nose V. 2012 2-12% (2), Herraiz M et al. 2007: 7% (9), Steinhagen E. et al 2012: 6.1% (10), Harb WJ and Sturgis EM 2009: 5%(11), Jarrar AM et al 2011: 2.6% (12). These incidences are considered high enough to justify screening for FNMTMC in all patients with FAP (Nose V 2011) by ultrasound neck examination and fine needle biopsy (FNB) even in small nodules (9).

Histological appearance of FAP-associated NMTC is similar in close relatives (13) and has a cribriform morular pattern with papillary architecture, morula formation, cribriform pattern with solid areas and spindle cells (7, 14, 15, 16). Pre-operative diagnosis may be suspected on fine needle biopsy which shows columnar cell with fine to granular chromatin, nuclear grooves, papillary and acinar fragments (17). Immunohistochemistry on FNB and histological specimens allows detection of accumulation of beta-catenin in cytoplasm and nucleus which is characteristic for APC mutation (18).

The known association between FAP and NMTC allows an earlier diagnosis by screening for thyroid cancer in FAP-confirmed patients and an earlier diagnosis of FAP in patients with cribriform morular variant of papillary thyroid carcinoma(13). Cribriform morular variant of FAP-associated thyroid carcinoma usually has an indolent course, rare metastases and a good prognosis (2).

MATERIAL AND METHODS

Patients were investigated by fine needle biopsy, MRI imaging and tumor biopsy, (first case) and histological examination of colonic and thyroid tumors (first case) and histological examination of thyroid tumor (second case).

CASE PRESENTATION

Case no. 1. A male patient of 68 years with complains of alternative diarrhea and
constipation was submitted to colonoscopy in December 2011 in the Clinic of Gastroenterology of “St. Spiridon” University Emergency Hospital. At 30 cm from anal edge a semipediculated polyp was identified and removed. In the proximity of the hepatic angle of the colon a large polypoid tumor was found and a superficial biopsy was performed. Histological examination of both specimens performed in the Laboratory of Pathology of the same hospital showed tubular adenomatous polyps with polymorphic inflammation and absence of malignant lesions (fig. 1).

The patients postponed surgery until 2 month later when he was admitted in emergency in the I Surgery Clinic of the aforementioned hospital for diffuse abdominal pain and absent of intestinal transit for less than 24 hours. At physical examination a large, painful tumor mass was detected on the right side of the abdomen. Abdominal X-ray showed liquid and air levels suggesting an occlusive state and chest X-ray showed lung nodules with an appearance of metastases. Liver ultrasound detected multiple nodules also considered to be metastases from a colonic cancer. Physical examination also identified a firm thyroid nodule of 6 cm its largest diameter, belonging to the left thyroid lobe, with preserved mobility on the neck structures and absence of compressive symptoms. The patients were operated in emergency. During surgery a colonic invagination took place due to an intraluminal tumor of 11 cm. the largest diameter, situated in the proximity of hepatic angle. Right hemicolectomy and resection of 13 cm of the terminal ileon, and ileal-transversal anastomosis were performed. Most lymph nodes in the area were carefully removed. An extensive macroscopic of the surgical specimen showed a large polypoid tumor mass, partially ulcerated which in microscopic examination had fibroblastic axes covered by ovoid cells, plasmocytes and eosinophils. All lymph nodes removed showed only histiocytosis. The patient came after 8 week and his diagnosis of colonic carcinoma with liver and lung metastases was revised by the surgeons and their attention was directed toward the thyroid nodule as a possible carcinoma. This time, the thyroid nodule was larger, both thyroid lobes strongly attached to the trachea, and bilateral lymph node enlargement was detected by clinical examination and neck ultrasound. Fine needle biopsy brought small micropapillary structures, thyroid cells with large nuclei, nucleolus and cytoplasmatic intranuclear inclusions (fig. 2). The attempt to remove the tumor failed and only a large biopsy was possible. The diagnosis was papillary thyroid carcinoma (fig. 3). With the diagnosis of stage T4N1Mx papillary thyroid carcinoma, the patient was transferred to the Clinic of Endocrinology of the same hospi-
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tal. MRI examination confirmed the presence of a large thyroid tumor (7.2 x 4.5 x 3.5 cm), developed also between the thyroid and cricoid cartilages, infiltrating left vocal cord, the esophagus on a length of 13 cm, and muscles and fat around it. All lymph node compartments surrounding the thyroid presented enlarged lymph nodes between 1.2 and 7 cm (fig. 4). The hormonal profile of the patient was normal: TSH=2.86 μIU/ml, FT$_4$= 11.93 pmol/ml. In these circumstances the patient was placed on suppressive therapy with T$_4$ and X-ray therapy was indicated for palliation.

**Case no. 2**

During the time when the first described patient stayed in the Clinic of Endocrinology, his son of 40 years old was informed that he carries a certain risk to have a thyroid disease and asked for permission to be examined for that. A physical examination, a large thyroid nodule was found in the right thyroid lobe. The patient was not aware of it before examination. Neck ultrasound identified a large inhomogeneous nodule of 3.9 x 5.3 x 2.9 cm with high vascularity and microcalcifications. Important blood contamination made the FNB specimen inadequate. The patient was operated in the 1st Surgery Clinic and a total thyroidectomy was performed. A postoperative bleeding was successfully solved.

The pathological examination described on a background of colloid goiter a multi-
centric papillary carcinoma with psammomas infiltrating the thyroid, without extension beyond the thyroid capsule. The tumor presented solid or cribriform areas and morula formation. Papillary cancer areas were found in the controlateral lobe (fig. 5 a, b). Immunostaining for HBME$_1$ was positive in 75% of tumor cells in their luminal pole, without basolateral membrane staining (fig. 5 c). 25% of cells of the cribriform and solid areas were also positive for HBME$_1$. The immunostaining with bcl$_2$ was positive in 100% of tumor cells (fig. 5 d). Histopathological staging of the disease was pT3Nx-G1. The pathologist conclusion was that the aforementioned characteristics are those familial forms of papillary thyroid carcinoma.

The patient received a radioiodine dose of 70 mCi for ablation. Before ablation his hormonal profile showed: TSH=66.8 μIU/ml, thyroglobulin=16.5 ng/ml and antithyroglobulin antibodies: 22 IU/ml. Post ablation scan detected radioiodine uptake in the thyroid bed. After radioiodine ablation the patient receives suppressive
therapy with 150 μg of T\textsubscript{4}. The colonoscopy performed two month showed that patient had no colonic polyposis. Careful ultrasound neck examination of his sister revealed no thyroid abnormalities.

DISCUSSION

In our knowledge, this is the first case of familial nonmedullary thyroid carcinoma (papillary carcinoma) reported in our setting. The reported cases have some typical features of FAP-associated papillary thyroid carcinoma and some particular characteristics. The proband case seemed to have an attenuated form of FAP (AFAP) with late onset of the disease and only a few polyps, proximally situation of polyps and infrequent rectal involvement as this form was defined by Half E. et al (6). The course of thyroid cancer in the proband was indolent for a very long time as mentioned for FAP-associated PTC by Cetta (16) and Ito (19), but suddenly it turned into an aggressive form with local invasion, lymph node metastases and distant lung and liver metastases as seen in the non syndromic FPTC (2, 20).

The typical histology of cribriform, morular variant of PTC, multicentricity and bilateralism (2, 15, 16) were seen in the second case. The tumor lost the affinity for HBME1 and preserves its immunostaining with bcl\textsubscript{2}. After Nasr (21), only luminal staining for HBME1 without basolateral staining is considered to be negative for HBME1 immunostaining. These features along with presence of AFAP and papillary carcinoma in the father raise the possibility that thyroid cancer could occur before adenomatous polyposis in this particular case.

The occurrence of the disease in males (father and son) could be also considered particular features because FAP-associated thyroid cancer occurs especially or almost exclusively in women at younger age (12).

The phenomenon of “genetic anticipation” defined as “occurrence of a genetic disease at progressively younger age and with increase aggressiveness in successive generations” described by Mc Innis (1996, quoted 22) for pure, nonsyndromic familial thyroid carcinoma was seen in the second reported case. Although after a long indolent course, the diagnosis a thyroid cancer was made at the age of 68 in the father and at the age of 40 in the son.

The most important point was in our cases the earlier detection of thyroid cancer in the son, allowing an adequate management of the disease and an expected good prognosis.

CONCLUSIONS

The occurrence of a simultaneous thyroid cancer in a patient with adenomatous polyposis must be suspected at the time of diagnosis of colonic disease.

Immediate screening for thyroid cancer must be performed in all first-degree relatives of patients with FAP by neck ultrasound and FNB if possible, allowing an earlier detection and a better prognosis of the thyroid disease.

REFERENCES


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