

THYROID NODULES IN PATIENTS WITH NEUROENDOCRINE TUMORS - TWO CASE REPORTS

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REZUMAT

Nu există suficiente date în privința tumorilor tiroidiene la pacienții diagnosticați cu tumori neuroendocrine, despre care se știe ca având un fond genetic complex, încă incomplet elucidat. Prezentăm cazurile a 2 pacienți cu tumori neuroendocrine la care s-a diagnosticat și un nodul solitar tiroidian. Deși prima suspiciune a fost de metastază tiroidiană, puncția cu ac fin, ca și examenul histo-patologic postoperator au arătat o patologie tiroidiană intrinsică. Primul caz este al unei paciente de 59 ani, care a suferit în urmă cu 1 an spleno-pancreasectomie pentru carcinom neuroendocrin bine diferențiat. În timp ce markerii neuroendocrini au fost crescuți postoperator, s-a diagnosticat un nodul tiroidian de 3 cm. Puncția cu ac fin a arătat epiteliu hiperplastic folicular. Examenul histologic a descris aspect de adenom microfolicular trabecular, embriofetal. Al doilea caz este al unui pacient de 51 ani, care a suferit hemicolectomie dreaptă pentru tumoră neuroendocrină de valvă ileocecală, la vârsta de 47 ani. Indexul PCNA a fost mare (50-60%). Nu s-a înregistrat sindrom hormonal de-a lungul a 4 ani de evoluție, dar s-a diagnosticat un nodul tiroidian stâng de 1 cm, la care examenul histopatologic postoperator a stabilit diagnosticul de carcinom papilar.

Cuvinte cheie: adenom folicular, carcinom papilar, tumoră neuroendocrină

ABSTRACT

There are no special data related to the thyroid tumors in patients diagnosed with neuroendocrine tumors, which are known to have a complex genetic background, yet incompletely elucidated. We present two patients known with entero-pancreatic tumors who were diagnosed with a solitary thyroid nodule. Also the first suspicion was a metastasis of the primary tumor, the fine needle aspiration biopsy (FNAB) and later the anatomical report after surgery pointed an intrinsic thyroidal pathology. The first case, a 59-years old female has one year history of pancreatic and spleen resection for well differentiated neuroendocrine carcinoma. While having high serum neuroendocrine markers after surgery, a left thyroid node of 3 cm is found. The FNAB suggested hyperplastic follicular epithelium. The pathological exam after surgery found a micro-follicular and trabecular embryo-fetal adenoma. The second case, a 51-years old male patient suffered a right hemicolectomy for neuroendocrine tumor of ileocecal valve at age of 47. The PCNA index was high (of 50-60 %) with no hormonal syndrome for 4 years, when a left thyroid nodule of 1 cm was discovered. The histological exam revealed a papillary carcinoma.

Key Words: follicular adenoma, papillary carcinoma, neuroendocrine tumor

INTRODUCTION

Genetic cancer susceptibility is more frequent and more variable in tumors of endocrine organs than in any other category of human neoplasm. An even more complex situation is registered in the case of neuroendocrine tumors.¹

Thyroid nodules are a usual occurrence (of 4% up to 10% of population), especially in endemic areas, with an age-related incidence; one tenth up to one third of them might be malignant.² A higher frequency of thyroid cancer is related to radiation exposure, but the increasing prevalence of thyroid incidentalomas is probably the effect of a larger access to health care.³ The patients with neuroendocrine tumors could have a higher risk of a second neoplasm, on a genetic background. We present two sporadic cases in which a second tumor was found, but with no particular phenotype connected to the originating neuroendocrine tumor.

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CASE REPORTS

The first patient was a 59-years old female, known with arterial hypertension for the last 6 years. One year ago she presented abdominal diffuse pain associated

with weight loss (10 kg/2 months). The abdominal ultrasound examination discovered a pancreatic solid tumor of 9 cm, associated with mesenteric adenopathies. Pancreatectomy at the body and tail level and splenectomy were performed. Secondary diabetes mellitus was registered. The pathological report revealed trabecular and alveolar microscopic structure with rare mitosis (2-3/10 HPF) and lymph nodes invasion at the spleen hill (stage IIIb: T4N1M0).⁴ The tumor cells showed positive immuno-staining for chromogranin A, synaptophysin, neuronal specific enolase, vimentin and CK 19. Based on these, diagnosis of well differentiated pancreatic neuroendocrine carcinoma was established. After surgery, the abdominal and thoracic computed tomography showed no other tumors or metastasis. On admission, the neuroendocrine markers revealed high serotonin of 492 ng/mL (normal between 40 and 200 ng/mL), slightly increased serum chromogranin A of 114 ng/mL (normal between 40 and 100 ng/mL) and normal 24-h urinary 5-hydroxy indolacetic of 2 mg/L (normal between 1 and 10 mg/L). Because of hormonal secretion (yet asymptomatic), therapy with Octreotidum LAR 20 mg/month was started. Three months after initiation, the neuroendocrine markers became normal. Also the general physical exam was normal, but a left thyroid nodule of 3 cm was discovered. The thyroid function, the thyroid antibodies and serum calcitonin were normal. The ^{99m}Tc Technetium thyroid scan revealed cold inferior left nodule. (Fig. 1) The ultrasound guided fine-needle aspiration biopsy (FNAB) showed hyperplastic multiple-layers follicular epithelium of trabecular type, with nuclear clearing and proliferate risk. Total thyroidectomy was performed. The pathological exam pointed micro-follicular and trabecular embryofetal adenoma with micro-hemorrhages. Thyroid substitution was started.

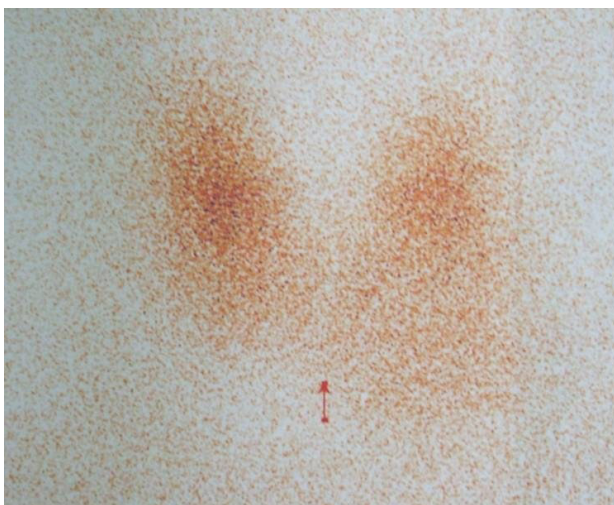


Figure 1. ^{99m}Tc Thyroid Scan: cold inferior left node.

The second patient was a 51-years old male patient, who suffered 4 years ago a right hemicolectomy with L-T ileotransverse anastomosis. The onset was with abdominal pain, intestinal transit disturbances. The histological exam showed a polypoid tumor of 4 cm, at the level of ileocecal valve, with local invasion of the wall. Two of the lymph nodes had metastasis, but no other metastases were further found (stage IIIB: T₃N₁M₀).⁴ The pathological evaluation showed ulcerated intestinal carcinoid. (Fig. 2)

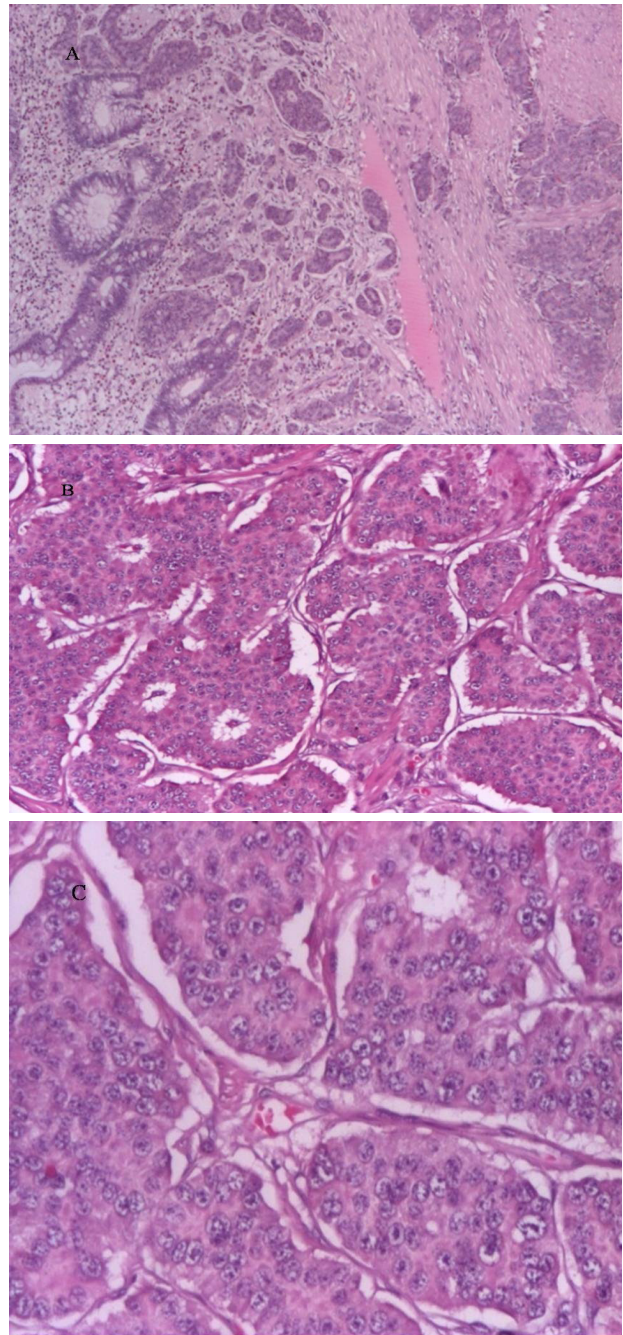


Figure 2. Histological Exam- hematoxylin eosin: Carcinoid of ileocecal valve (A.40x; B.100x; C.200x).

The immunohistochemistry showed positive reaction for chromogranin A, NK1, negative for

synaptophysin, CD56. The PCNA proliferation marker was high (50-60%). (Fig. 3)

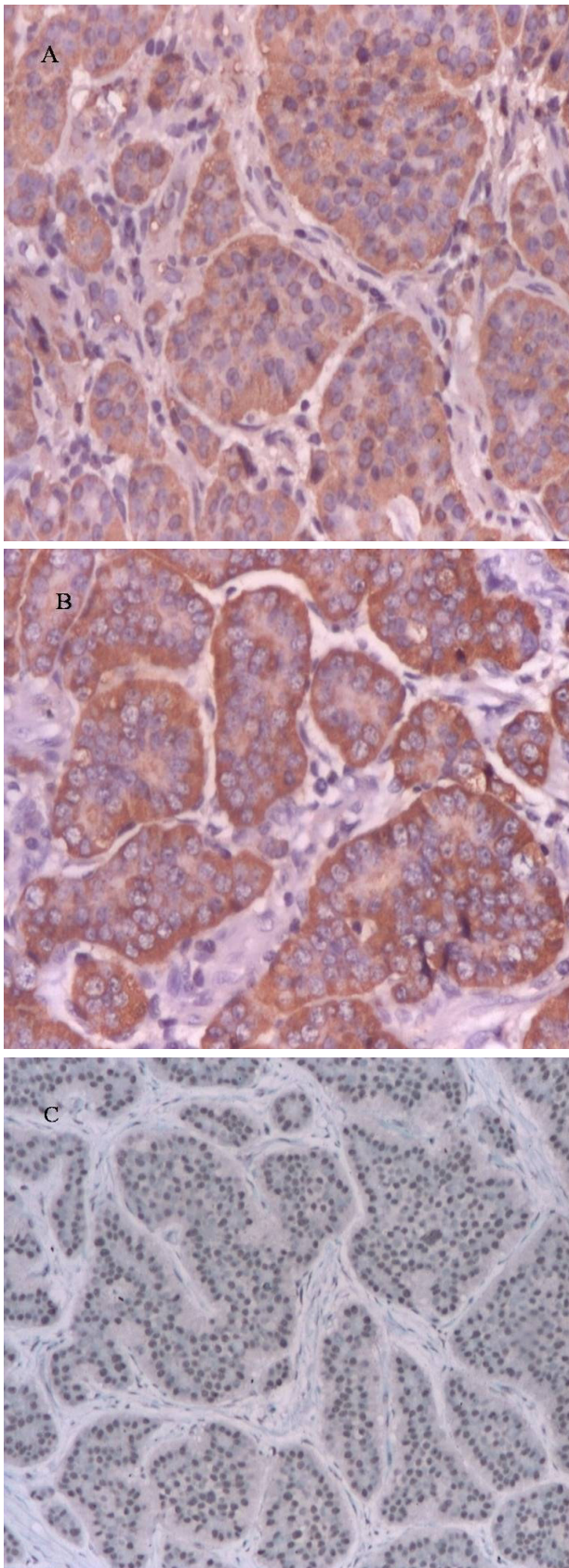


Figure 3. Immunohistochemistry: Carcinoïd of ileocecal valve. A. Chromogranin zonal + 200x. B. NK1 diffuse + 100x. C. PCNA of 50-60% 200x.

For four years he was followed-up by neuroendocrine markers, which were negative. On admission, the clinical exam discovered a left thyroid nodule of one cm. The serum TSH, thyroid antibodies and calcitonin were normal. The FNAB suggested papillary carcinoma, which was later confirmed by the histological report after surgery (a tumor of 1.2 by 0.8 cm with marginal invasion was removed). Based on patient's age, tumor size, and histological aspects, the patient had intermediate risk of recurrence.⁵ The thyroglobulin after suppression therapy withdrawal was 0.2 ng/mL. The thyroid ¹³¹Iodine scan was positive for thyroid and negative for the rest of the body. Adjuvant radioiodine remnant ablation was used (100mCi). Further risk-adapted management is necessary.

DISCUSSIONS

In the first case, the FNAB suggested a follicular neoplasm, which turned out to be benign. The cut-off between benign or malign is made by capsular or vascular invasion, that can only be pointed by histological exam.⁶ Even the FNAB cannot distinguish between follicular cancers or adenomas and other procedures as core-needle biopsies provide no additional diagnosis before surgery.⁷ The benign aspect is confirmed after surgery in more than one third of cases if atypia is not found in FNAB, as in our case.⁸ Generally, the follicular cancer is found in 8 up to 30% of all follicular neoplasms.^{9,10} A lower chance of malignancy have females and patients older than 45 years, or if the nodules are smaller than 4 cm, as in the presented case.¹¹ Both the pancreatic tumor and the follicular adenoma had trabecular growing structure. The pancreatic neuroendocrine tumors are usually larger than 5 cm, as here, but located mostly in the pancreatic head. The nesting type is much more frequent than trabecular structure.¹²

The second case refers to papillary carcinoma, which is the most frequent thyroid cancer.¹³ By 2005, men were diagnosed with thyroid cancer at a rate of 5.1 per 100.000, up from 2.5 in 1988.¹⁴ There was also an average annual 9.9% increase of small tumors.¹⁵

We have presented patients having two neoplasms, suggesting a possible connection. It is known that in the digestive tract, 5 up to 10% of neuroendocrine tumors have a hereditary background.¹ But most of the cases are sporadic, with so called "suspected hereditary background".¹ Data regarding tumors association are limited. We raise the question of a thyroid neoplasm link, but it is also possible an epidemiological overlap, even if the two patients came from non-endemic area. Studies suggested an increased risk

of a second neoplasm after a first neuroendocrine tumor. Some authors have found that 36% of patients with ileal tumors have an associated malignancy.¹⁶ Endogenous or environmental risk factors might also be involved.¹⁷ Among them, genetic background suggested by familial clustering is considered. One study found 3.7% of patients with neuroendocrine tumors as having a first degree relative with the same malignancy.¹⁸ The observation was confirmed by a nation-wide epidemiological Swedish study.¹⁹ Similar large population studies from Denmark and USA failed to confirm the increased cancer risk.^{18,20}

CONCLUSION

The neuroendocrine tumors field is still a complex area. If there is a high risk of a second neoplasm, especially thyroidian, it is still a matter of debate.

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