CASE REPORTS

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The immunohistochemistry aspects in two cases of neurofibromatosis-associated abdominal tumors

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Abstract

Type 1 neurofibromatosis associates various abdominal tumors as gastrointestinal stromal tumors, duodenal or pancreatic carcinoid, and adrenal tumors like pheochromocytoma. We present the immunohistochemistry report in two cases with different profile regarding the evolution. One case is a 7th decade women diagnosed with unilateral pheochromocytoma and GISTs, with a good prognosis after surgery. The other case is a 41-year-old male diagnosed with duodenal metastatic somatostatinoma after an intestinal occlusive syndrome and later the hormonal profile leaded to the diagnosis of pheochromocytoma. The patient had a fulminate evolution within six months from diagnosis.

***Keywords*:** neurofibromatosis, immunohistochemistry, pheochromocytoma, somatostatinoma, GIST.

Introduction

The neurofibromatosis is a genetic disease that implicates beyond the aesthetic skin lesions, the presence of tumors with a various profile of aggressive behavior. Type 1 neurofibromatosis (NF) associates in 25% of cases gastrointestinal tumors as stromal (benign or malignant) or neuroendocrine tumors as duodenal (or pancreatic) somatostatin-rich carcinoid, and pheochromocytomas in more than 10% [1, 2]. The immunohistochemistry is a necessary evaluation of the tumors in order to have an early diagnosis of those fulminate cases to be treated properly, if it is possible.

Patients, Methods and Results

Case No. 1

N.E., 61-year-old female, has multiple diffuse skin neurofibromas since early childhood with progressive development during the years. Also, she has five café au lait spots, the largest of 5 cm on the leg (Figure 1). She did not know her medical family history and she has no children. On her 7th decade of life, she had a hypertensive attack. An endocrine evaluation pointed a left pheochromocytoma of 1.12 by 0.81 cm as the plasma metanephrines and normetanephrines were repeatedly high (three times as normal) and also increased serum chromogranin A was found.

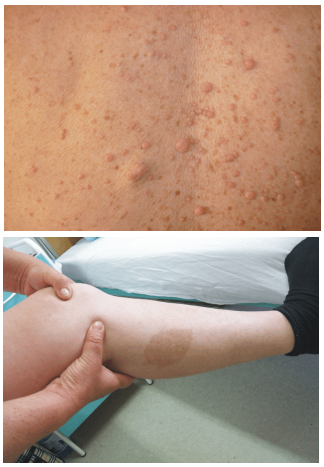

Figure 1 – ***(a) Back of the thorax: multiple neurofibromas. (B) Café au lait spot.***

Moreover, the abdominal computed tomography (CT) revealed two duodenal tumors of 5.61 by 6.29 cm,

with a cystic component of 2.73 by 3.01 cm and another of 5.44 by 3.79 by 3.98 cm with necrosis. The surgical trans-abdominal approach was performed for all the tumors. The intestinal tumors were diagnosed as gastrointestinal stromal tumors (GIST). The tumors were benign, with a mixed structure: solid–colloid. The immunohistochemistry (IHC) was positive for CD117, CD34, and ACT into the vessels, and negative ACT into the tumor was found (Figure 2). The adrenal tumor was diagnosed as pheochromocytoma, with IHC specific for a neuroendocrine phenotype like positive reaction for S100 and CROMO (Figure 3). The Ki67 was lower than 1%. After surgery, the plasma metanephrines and normetanephrines normalized. Also, the blood pressure was within the normal limits. The patient was followed up for more than a year and remained asymptomatic.

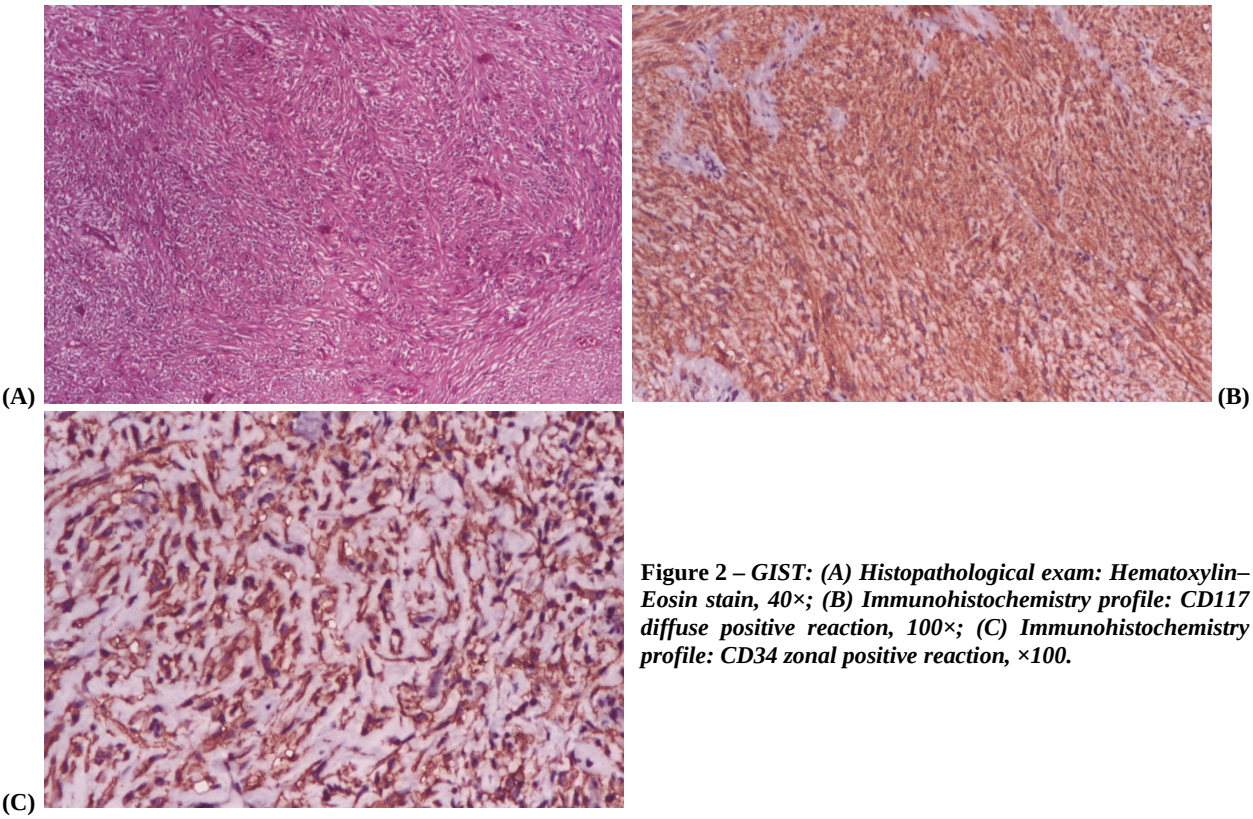

Figure 2 – ***GIST: (A) Histopathological exam: Hematoxylin–Eosin stain, 40×; (B) Immunohistochemistry profile: CD117 diffuse positive reaction, 100×; (C) Immunohistochemistry profile: CD34 zonal positive reaction, ×100.***

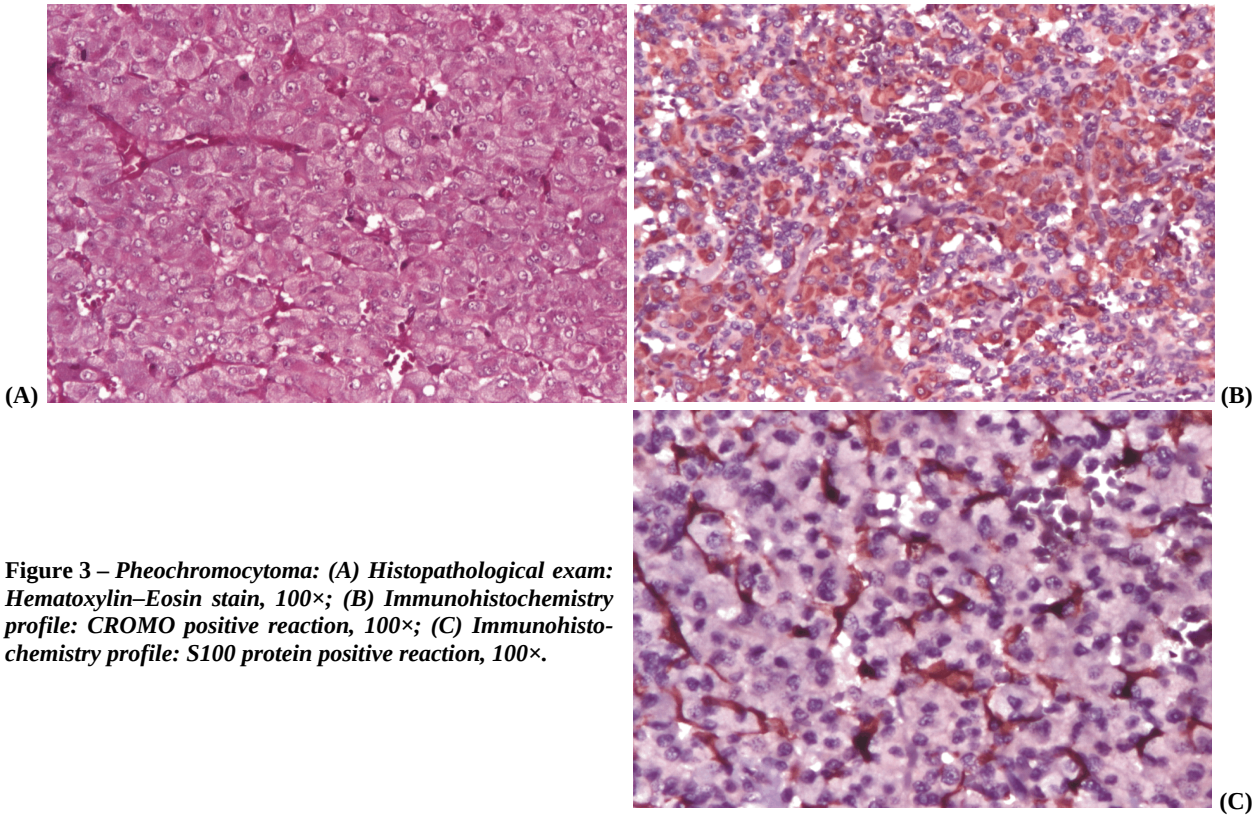

Figure 3 – ***Pheochromocytoma: (A) Histopathological exam: Hematoxylin–Eosin stain, 100×; (B) Immunohistochemistry profile: CROMO positive reaction, 100×; (C) Immunohistochemistry profile: S100 protein positive reaction, 100×.***

Case No. 2

D.N., 41-year-old male patient, has a 15 years history of mild arterial hypertension (up to 165/100 mmHg), controlled by low doses of antihypertensives. The family history is irrelevant. He has no children. He associates multiple diffuse neurofibromas and six thorax cutaneous brown spots (Figure 4).

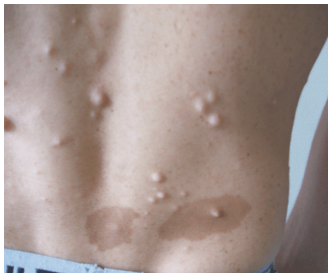

Figure 4 – ***Lumbar neurofibromas and café au lait spots.***

He also has a history of a tibia malformation since childhood. In May 2010, he suffered an emergency surgery for superior occlusion, manifested as progressive weight loss and abdominal pain. The CT showed a tumor on the level of the duodenum and the first jejunal loop. During surgery, no major complications were registered. The surgical exploration showed multiple metastasis of less than 1 cm into the peritoneum. The enterectomy of the first jejunal loop and the third duodenal part resection were performed with a T-L anastomosis. The pathological exam and the IHC showed a neuroendocrine tumor of 2 cm and four of the 12 nodes with metastasis (pT3N1M1, G3). The IHC pointed a positive reaction for SYN, SOMATO, CK, CDX2 (in some areas), negative for CROMO and CK, and a Ki67 of 10% (Figure 5).

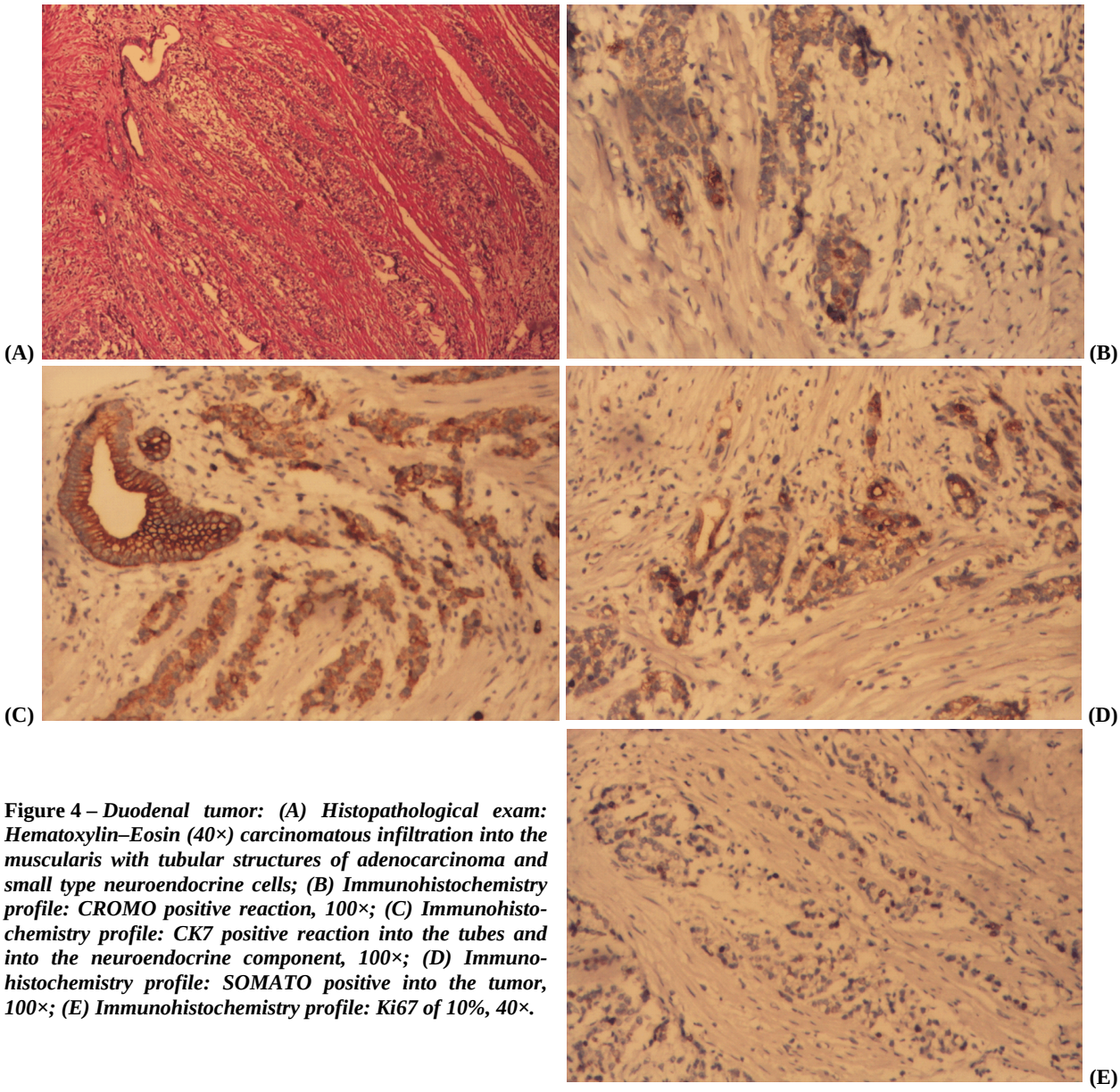

Figure 4 – ***Duodenal tumor: (A) Histopathological exam: Hematoxylin–Eosin (40×) carcinomatous infiltration into the muscularis with tubular structures of adenocarcinoma and small type neuroendocrine cells; (B) Immunohistochemistry profile: CROMO positive reaction, 100×; (C) Immunohistochemistry profile: CK7 positive reaction into the tubes and into the neuroendocrine component, 100×; (D) Immunohistochemistry profile: SOMATO positive into the tumor, 100×; (E) Immunohistochemistry profile: Ki67 of 10%, 40×.***

The endocrine profile showed high metanephrines and normetanephrines suggesting a pheochromocytoma (Table 1).

Abdominal CT-scan showed two right adrenal tumors of 3.33 by 3.06 and 4.58 by 3.66 cm. Also, a small left adrenal tumor of 1.17 by 0.7 cm was found. The cerebral

MRI showed a polycystic tumor of 3.2 by 1.8 cm with edema and osteolysis in surrounding areas, suggesting a malignant profile. The pheochromocytoma was suspected but also adrenal metastasis might have been presented. The patient delayed adrenalectomy and he died six months later after a bowel occlusive syndrome (Figure 6). It was not possible to appreciate if there were appendicle metastasis or another primary tumor. No autopsy could be performed.

Table 1 – *Endocrine profile*

Hormone	Value	Normal
Calcitonin [pg/mL]	3.15	<13
Carcinoembryonic antigen [ng/mL]	1.5	<3.4
Neuronal specific enolase [ng/mL]	24.1	<17
Chromogranin A [ng/mL]	132	<100
Serotonin [ng/mL]	283	40–200
5HIIA [ng/mL]	3.52	1–10
Normetanephrines [pg/mL]	532 repeated 460	15–100
Metanephrines [pg/mL]	201 repeated 149	10–90

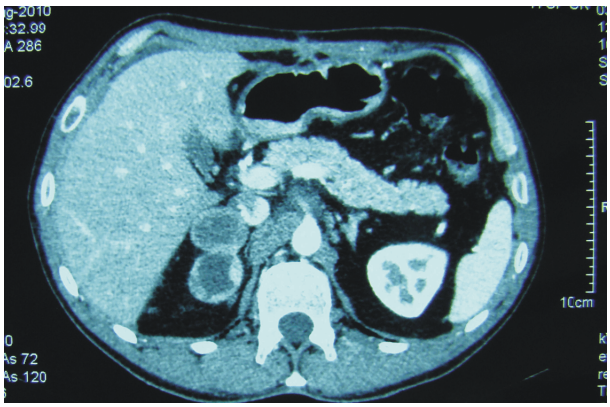

Figure 6 – *Abdominal CT: right adrenal tumor.*

Discussion

The GISTs are often associated with skin neurofibromas (criteria in type 1 neurofibromatosis phenotype), possible due to the same genetic base as neurofibromas [3]. The most important mutation is related to the succinate dehydrogenase SHD enzymes, especially subunit B [4]. Both our cases had a negative family history. Neither did we perform genetic tests. The type 1 neurofibromatosis is an autosomal dominant disease affecting one in 3500 persons but half of cases are sporadic as apparently our two cases. A wide variation of phenotype is presented regarding the skin and the visceral dysfunctions and also new mutations are continuously describing on NF1 gene from chromosome 17q11.2 [5]. In the first case, the GISTs were an incidental finding during the CT, as it was the pheochromocytoma in the second one. Generally, the adrenal tumors may remain asymptomatic even in case of high dimensions [6]. Also, they may behave with no signs or symptoms despite the excessive hormonal secretion or these are underestimated as it was the long time hypertension of the male patient [7]. The histological and IHC aspects were extremely relevant in the first case were the CT profile first suspected an adrenal metastasis. Also, the link between neuroendocrine profile of a tumor and its metastasis or, on the other hand, the presence of the two distinct synchrony tumors is confirmed by IHC [8]. This was not the case in the male patient, after the first surgery. In the first case, the IHC also helped the differential diagnosis of the GISTs with a duodenal carcinoid or a leyomyoma that may also be associated with NF [9]. The aggressive histological profile of a GIST based on number of mitosis, Ki67, etc. indicates starting the adjuvant chemotherapy or tyrosine kinase inhibitors treatment [4]. The GISTs have been included in different phenotypes as Carney triad (including extra-adrenal paraganglioma and pulmonary chondroma). An IHC study in 104 GISTs detected KIT in 100% of cases; CD34 in 75%; PDGFRA in 90% [10]. In our case, CD117 and CD34 were positive. The GISTs from Carney triad compare to sporadic tumors are more frequent in young females, have epithelioid cell predominance, multifocality, frequent lymph node metastasis, and serial tumor occurrence [10]. Also, GISTs have been described in dyad with paragangliomas in NF [4].

Neurofibromatosis associates other abdominal tumors beside of the intestinal tumors. The most common example is the neuroendocrine tumors especially pheochromocytoma but also somatostatinoma as a more rare event. Also, adrenal carcinomas have been described [4]. A few cases of thyroid medullar carcinoma had also been reported in NF1 and more frequent in NF2 [11]. In the von Recklinghausen's disease, non-endocrine phenotypes may include interstitial lung disease, found in up to 20% of NF1 adults [9]. The eye changes are also hallmarks in NF but there were not significant changes in both our cases. The IHC profile is imperative in gastrointestinal tumors associated with neurofibromatosis to appreciate the neuroendocrine profile or the stromal one. The neuroendocrine phenotype is sustained by CROMO, SYNAPTO, NSE (neuronal specific enolase), and SOMATO. The later marks the diagnosis of somatostatinoma with a very aggressive profile, as it was our second case. Type 1 NF is more frequent associated with duodenal *vs.* pancreatic somatostatinoma (43.2 *vs.* 1.2%) according to an evaluation of 173 cases [12]. Duodenal somatostatinoma mere 2% of small bowel carcinoids and 5 up to 10% of all duodenal tumors. The first case was described by Kaneko, in 1979. A strong correlation to type 1 NF needs to be considered [14]. The first cases regarding the association of neurofibromatosis, pheochromocytoma and somatostatin-rich duodenal carcinoid tumor as our second case were published in the 80's [13]. The Ki67 value in the case of the neuroendocrine tumor is a very relevant marker of proliferation, being introduced as an essential tool in the classification of the neuroendocrine tumors. The somatostatinoma was an IHC finding in the second case based on SOMATO positive reaction because the patient did not have the so-called somatostatinoma syndrome. Also, Ki67 indicated a medium proliferation profile, the evolution was extremely rapid, more likely related to the fact that somatostatinoma may behave as an extremely aggressive neoplasia. Also at the moment

of diagnosis, distant metastasis as peritoneal and possible cerebral were presented, indicated a spread disease.

Pheochromocytoma is presented in 0.1 up to 5.7% of patients with NF1, and 10% may be bilaterally [2]. In our second case, we could not have the confirmation of such case. Also, an adrenal metastasis could have been associated. The pheochromocytoma from NF1 may have a histological variant called composite pheochromocytoma (including ganglioneuroma elements). The serum chromogranin A is typically high in pheochromocytoma as a neuroendocrine marker of the tumor. There is no quantitative correlation with the positive reaction of CROMO at IHC.

Conclusions

We appreciate the immunohistochemistry evaluation as essential in a more precise diagnosis of the abdominal tumors associated with type 1 neurofibromatosis as pheochromocytoma, GISTs, somatostatinoma, proving an essential tool in prognosis evaluation and follow-up of the patients.

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