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Neuroendocrine tumors and their association with rare tumors: observation of 4 cases

F. CIRILLO

Department of General Surgery, General Surgery Unit, Rare Hormonal Tumors Group, AO Istituti Ospitalieri, Cremona (Italy)

Abstract. – *Purpose:* **Neuroendocrine tumors are rare neoplasms, with an incidence of about 1/100,000/year. The association between digestive neuroendocrine tumors and epithelial tumors is known, accounting for about 10% of cases, whilst in a very small number of other cases an association with other low incidence tumors has been observed.**

Methods: **During the past 19 years the Rare Hormonal Tumors Group of the Istituti Ospitalieri in Cremona, Italy has observed 300 patients affected by neuroendocrine tumors. We report here on four cases in which there was an unusual association with other rare neoplasms.**

Results: **Overall, four of the 300 observed cases (1.3%) showed an unusual association with rare nonepithelial neoplasms: (1) gastric carcinoid and glioblastoma multiforme; (2) Merkel cell tumor and squamous cell carcinoma of the skin; (3) medullary thyroid carcinoma, yolk sac tumor of the testis and gastrointestinal stromal tumor (GIST); (4) gastric carcinoid and GIST.**

Discussion: **There cases are of interest not only from an epidemiological point of view, but also offer insight into possible geno-phenotypical implications. The c-kit expression, typical of GISTs but observed also in other epithelial and neuroendocrine tumors, not only broadens the possibility to gain insight into the carcinogenesis of these neoplasms, but also opens the field to possible new therapeutic opportunities using multitargeted molecules. The contemporaneous presence of other lesions, such as the Merkel cell tumor and the squamous cell carcinoma of the skin can be interpreted as an answer by the cell to the same mutagenic stimulus. In other cases, where a possible link is not yet found which could explain the synchronism or metachronism of low incidence neoplasms, it remains possible that the associations are entirely coincidental. We await for new instruments which could help us demonstrate the possible relationships between low incidence neoplasms.**

Key Words:

Gastrointestinal stromal tumor, Neuroendocrine tumor, Gastric carcinoid tumor, Merkel cell carcinoma, Medullary thyroid carcinoma, Squamous cell carcinoma, Yolk sac tumor, Glioblastoma multiforme, c-kit, Synchronous neoplasms.

Introduction

Neuroendocrine tumors are rare neoplasms, having an average clinical incidence of about 1 case per 100,000 of the population per year, with variations due to the histotype. In most cases these tumors are characterized by a low level of malignancy and long survival. Exceptions are malignant forms where the neoplasm metastasizes towards the regional lymph nodes and commonly towards the liver (15-20%) and undifferentiated forms with a high degree of malignancy[1].

From a clinical point of view neuroendocrine tumors can be divided into two different groups: *functional tumors (secreting or symptomatic, about 20% of cases)* and *nonfunctional tumors (not secreting, asymptomatic)* according to their capacity to produce and secrete peptidic substances that cause non-specific symptoms that are nevertheless strongly characteristic for this group of neoplasms.

A complete updated anatomic-pathological revision distinguishes these neoplasms according to their different degree of malignancy, where the traditional morphological criteria (histotype and grading) are now associated with new immunohistochemical diagnostic parameters about the biological activity of the tumor[2].

Patients and Methods

The Rare Hormonal Tumors Group at the *Istituti Ospitalieri* in Cremona, Italy monitors the incidence of unusual neuroendocrine tumors. Dur-

Corresponding Author: Fernando Cirillo, MD; e-mail: f.cirillo@neuroendocrini.it

ing the last 19 years, as of the 31st of December 2008, our Group has observed 300 neuroendocrine tumors, 220 of which were gastroenteropancreatic, 27 bronchial, 26 Merkel cell tumors, 9 carcinomas with neuroendocrine differentiation, 8 pheochromocytomas, 7 medullary thyroid carcinomas, and 3 neuroendocrine carcinomas of the prostate. In 10% of cases we observed a rare association of a digestive neuroendocrine neoplasm with epithelial neoplasms,[3] and even less frequently (4 patients [1.3% of cases]) an association with nonepithelial neoplasms. In the latter category, the 4 cases involved: (1) type 1 gastric carcinoma and glioblastoma multiforme of the encephalon; (2) Merkel cell tumor and squamous cell carcinoma of the skin; (3) medullary thyroid carcinoma, gastrointestinal stromal tumor (GIST) and mixed germinal tumor of the testis; (4) gastric carcinoid and GIST.

Due to the infrequent and uncommon association, we believe it to be important to highlight the series described hereafter.

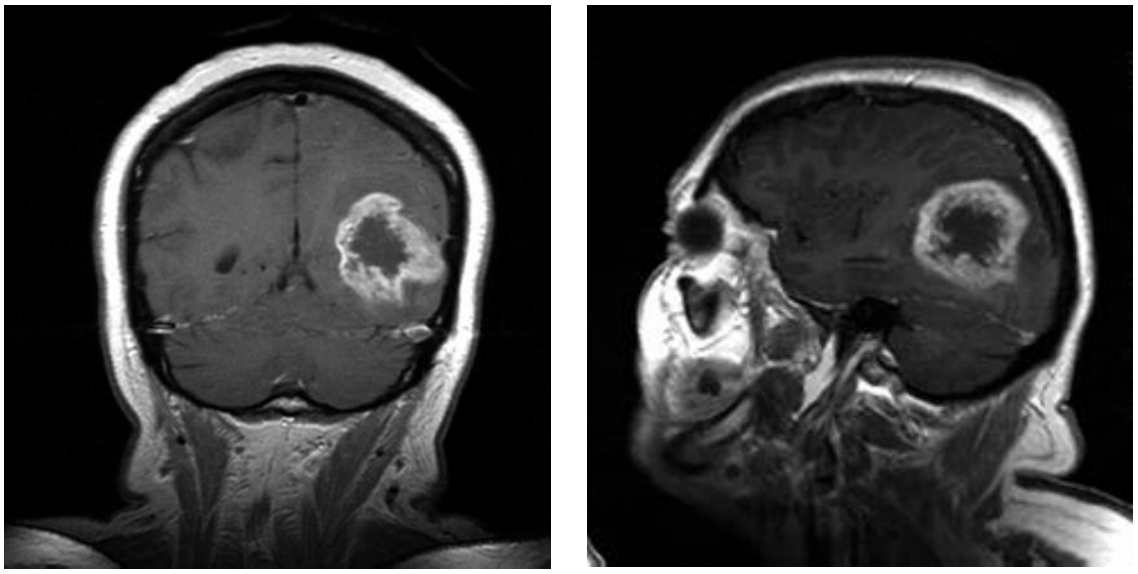
Results

Case 1

Case 1 was a female patient aged 65 who had type 1 diabetes and arterial hypertension treated with β-blockers. The patient had experienced abdominal colic pains for several months that were associated with sporadic episodes of biliary vomit. Abdominal computed tomography (CT) was performed, showing a surrenalic lesion to the right (10.7 × 7.7 × 8.3 cm), and its radiological appearance suggested a myelo-fibrolipoma. Amongst the blood chemistry tests, chromogranin A showed a value of 212 ng/ml (radioimmunoassay method), gastrin 1540 pg/ml, beta-human chorionic gonadotropin 1.57 ng/ml, calcitonin 20 pg/ml, and neuron-specific enolase (NSE) 19 ng/ml. Thyroid-stimulating hormone, parathormone, thyreoglobulin and thyroxine were all within the normal range. The urinary 24-hour values of vanillylmandelic acid and of 5-hydroxyindoleacetic acid were also within the normal range. The patient denied experiencing flushing, chronic diarrhea or dyspeptic symptoms that could indicate a neuroendocrine pathology, in particular a functional pheochromocytoma associated with the known hypertension or even multiple endocrine neoplasia (MEN). The patient underwent a right surrenalectomy and a cholecystectomy for biliary lithiasis, and histological examination confirmed a surrenalic myelolipoma and chronic cholecystitis. The post-operation blood chemistry continued to show high values for chromogranin A and gastrin (188 ng/ml and 1798 pg/ml, respectively), while control of arterial blood pressure was improved. Digestive endoscopy revealed a polypoid formation of about 1 cm in diameter at the antral-corpus boundary, with non-significant histological examination. We suspected the presence of an underestimated gastric carcinoid and the patient began treatment with the somatostatin analog, octreotide LAR, 20 mg every 28 days, in combination with lansoprazole, 30 mg twice daily. Six months later the chromogranin A and gastrin values were still high and for this reason the octreotide LAR dosage was raised to 30 mg every 28 days and lansoprazole was replaced by omeprazole at a dosage of 40 mg twice daily. A subsequent digestive endoscopy confirmed the presence of a simple hyperplasia of endocrine cells on the gastric fundum. Two months later the patient report disturbances in her speech and signs of ideomotor apraxia; for this reason cerebral CT and nuclear magnetic resonance (NMR) were performed, showing the presence of a large irregular solid lesion, supratentorial, on the left parietal occipital region, compatible with a glioblastoma multiforme (Figure 1). The patient underwent an open biopsy of the cerebral lesion, and histological results indicated a grade IV glioblastoma with weak and focal immunophenotypical expression of glial fibrillary acidic protein, no expression of p53 and a cell proliferation index (ki67 clone MIB1) equal to 10%. The patient commenced radiation treatment (30 Gy) associated with temozolomide, 75 mg/m^2/day. Unfortunately, death occurred 4 months later due to progression of the cerebral disease.

Case 2

Case 2 was a female patient aged 80 who had a raised and eroded pinkish lesion on the back of her right foot. The size of the lesion on presentation was 1.7 × 1.5 cm and had been increasing in the previous few months. The lesion was surgically removed under local anesthetic. Histological examination showed an ulcerated Merkel cell tumor infiltrating the reticular dermis up to the boundary with the hypodermis, associated with a squamous carcinoma at the early stages of infiltration, scarcely differentiated. There was no evidence of angioinvasivity. Immunohistochemical results were as follows:



A B

Figure 1. ***A, B,*** Nuclear magnetic resonance encephalon: oval lesion with irregular edges, 45 mm in diameter in the left parietal-temporal area. Significant peripheric edematous and central necrotic component.

chromogranin +; NSE +; synaptophysin +; ki67 (clone MIB 1) equal to 80% (Figure 2). Six months after the removal there are no signs of any local or remote relapse of the disease.

Case 3

Case 3 was a male patient aged 25 who had undergone total thyroidectomy for medullary thyroid carcinoma (Figures 3 and 4). At that time there was no germinal mutation in the RET gene, the pentagastrin test was negative and the patient received no ancillary treatment. Nine years later the patient approached his doctor due to a tumefaction of about 5 cm in diameter on the right testis (Figure 5), with subsequent orchiectomy. Histological results showed a mixed germinal neoplasm comprising 20% embryonal carcinoma and 80% yolk sac tumor, with evidence of Schiller Duval bodies and strong positivity on immunohistochemical analysis for alpha-fetoprotein, and metastatic involvement of the lymph nodes. The patient subsequently received ancillary PEB chemotherapy (cisplatin, etoposide, bleomycin) with the conventional pattern, for 3 cycles. During follow-up, tomography revealed a hypodense lesion about 3.5 cm in diameter on the lesser curvature (Figure 6) that was found on subsequent resection and histological examination to be a gastric GIST with low grade malignancy. Seventeen years after the thyroidectomy, high values of plasmatic calcitonin (992 pg/ml) and carcinoembryonic antigen (CEA) (9.9 ng/ml) were noted and the disease restaged (CT and NMR total body, ^{18}F-DOPA positron emission tomography [PET]-CT, ^{68}Ga-DOTATOC PET-CT). Evidence was found of a relapse of the disease on the neck and liver that was confirmed by histological examination. The patient has begun radiometabolic treatment with targeted molecules.

Case 4

Case 4 was a male patient aged 79 years who required emergency hospitalization due to a digestive hemorrhage of gastric origin, as confirmed by endoscopy. The hemorrhage could not be controlled despite multiple transfusions, necessitating a total gastrectomy. Macroscopic examination of the specimen removed showed a lesion 1 cm in diameter near the pylorus, under the gastric mucosa, whilst a whitish nodule about 0.5 cm in diameter and with a wood-hard consistency was found along the greater curvature, about 8 cm from the esophageal boundary. Histological examination of the pyloric lesion indicated a well differentiated neuroendocrine tumor with a low level of malignancy, with a proliferation index ki67 (clone MIB 1) equal to 2%.The overall clinical picture of the second lesion indicated instead a low-risk GIST, with positivity for CD 117 and CD 34, and a cell proliferation index equal to 1%. After a long rehabilitation period the patient was discharged under watchful care.

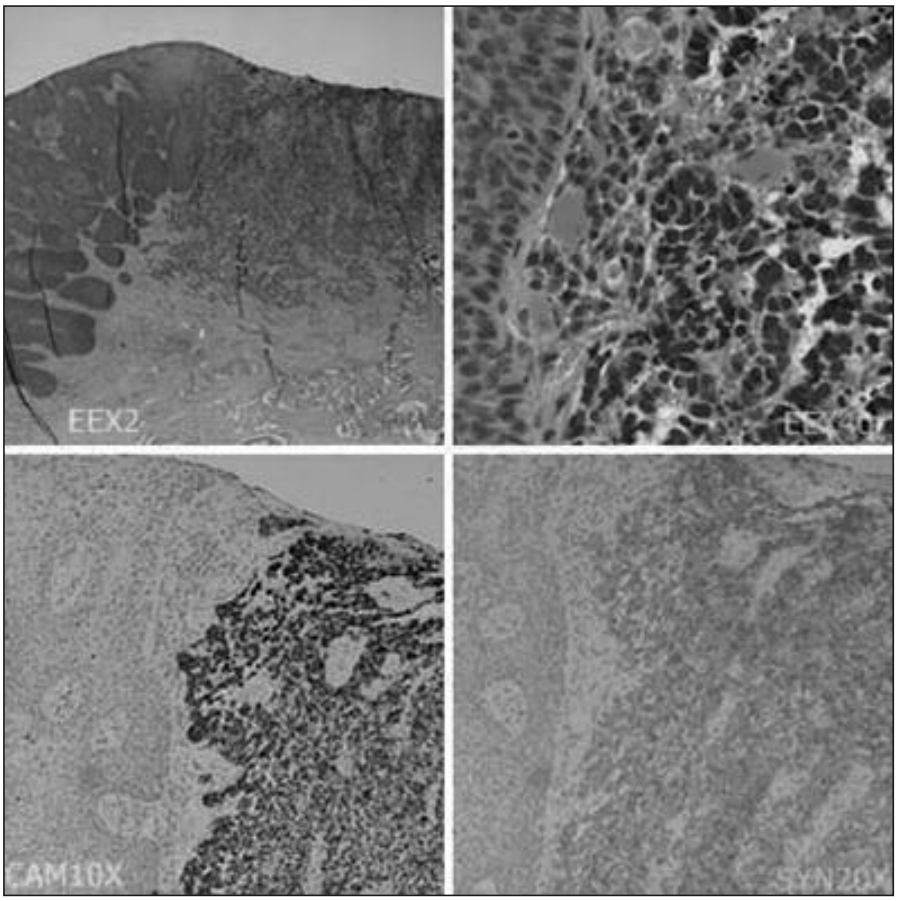
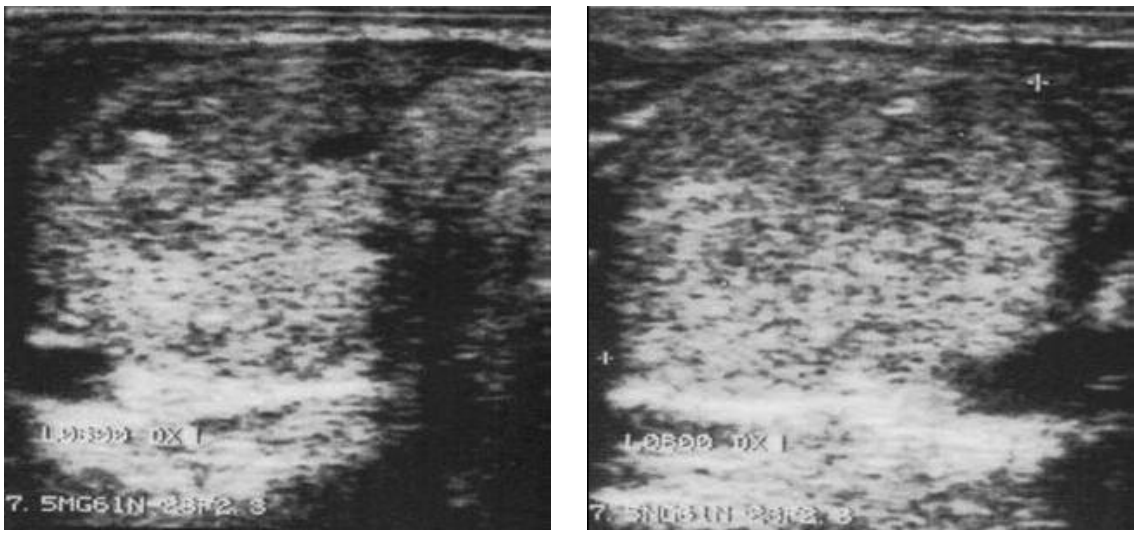


Figure 2. Merkel cell tumor and squamous cell carcinoma of the skin. Clockwise, from top to bottom: Merkel cell tumor in close proximity with squamous cell carcinoma of the skin (Haematoxylin-Eosin 2 ×), same frame with greater magnification (40 ×), evident expression for synaptophysin (20 ×) and for CAM 5.2 (10 ×) for the neuroendocrine portion.



A **B**

Figure 3. A, B, Echography of the thyroid showing enlarged dimensions to the right due to the presence of a solid formation with isoechogen echostructure, about 37 mm in diameter.

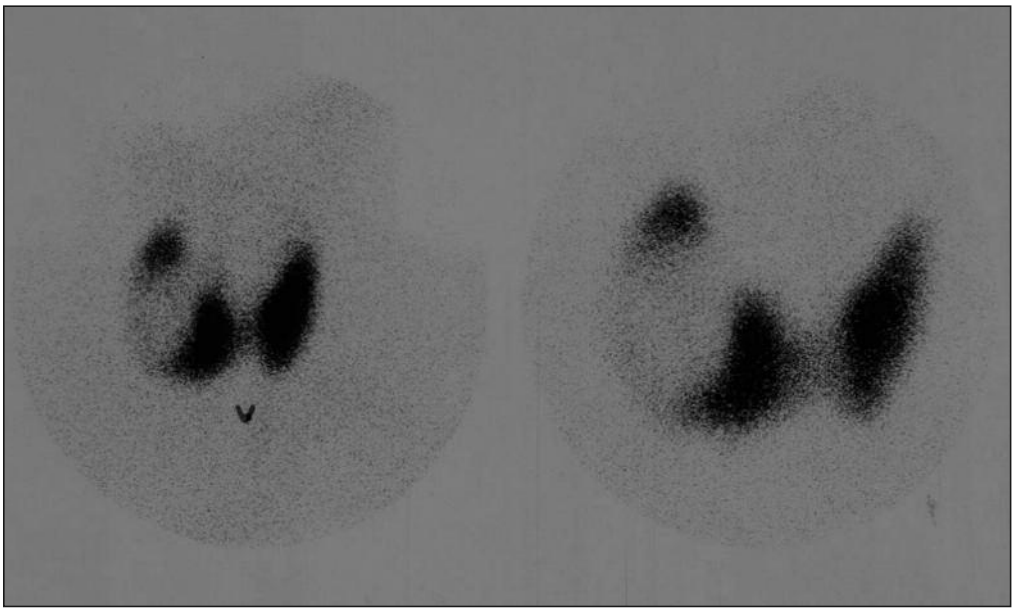


Figure 4. Scintigraphy of the thyroid with 99mTc showing enlarged right lobe, presenting a void of uptake of the marker at the lower-middle third, corresponding to a formation which can be locally felt by touch.

Discussion

Neuroendocrine tumors are rare and represent a group of neoplasms that is rather heterogeneous, characterized by an extremely variable and unpredictable evolution. Recently an increase in the incidence of these tumors has been observed, from 1.09 to 5.25/100,000/year in the period 1973-2004[4]. This increased incidence has been accompanied by an increase in survival, suggesting that neuroendocrine tumors have a greater prevalence than previously reported[4]. In 70% of the cases, neuroendocrine tumors are well differentiated, and are characterized by long

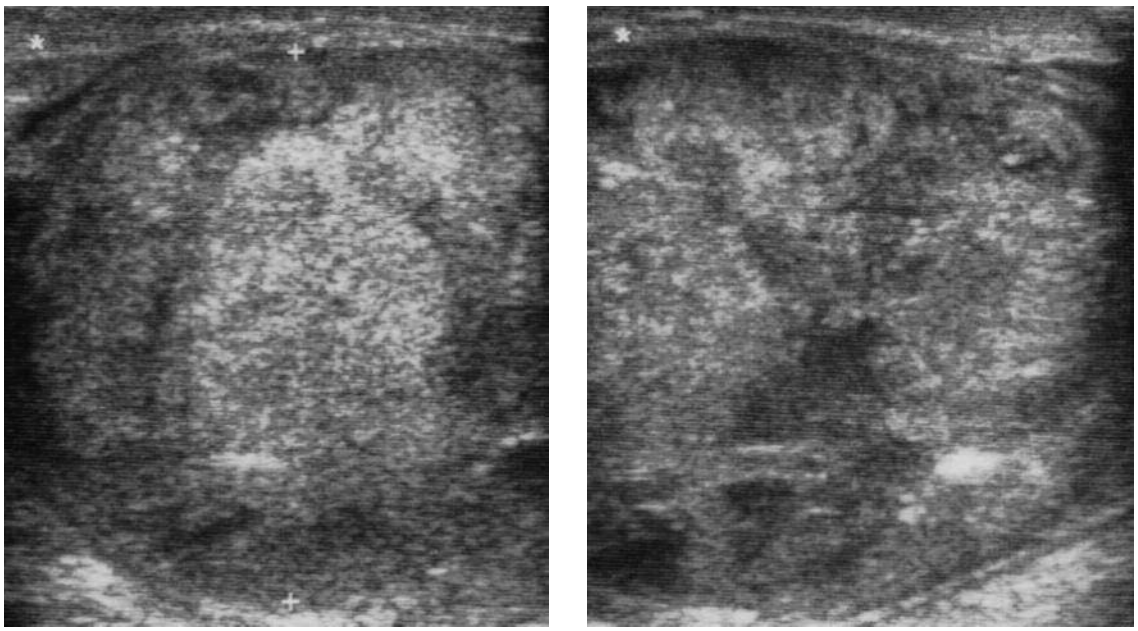


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Figure 5. ***A, B,*** Echography of the right testis showing a lesion of 5 cm in diameter, almost entirely overturning the right testis.

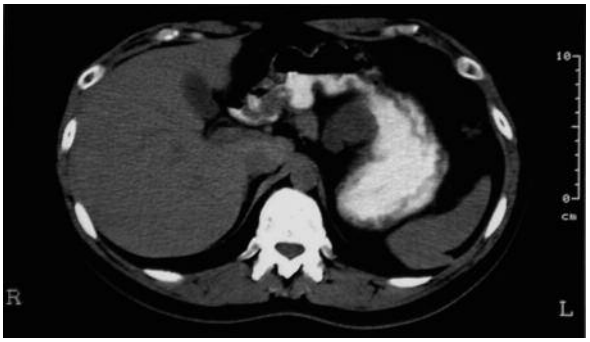

Figure 6. Abdominal computed tomography with contrast medium: density of soft tissue of about 3.5 cm in diameter along the lesser curvature of the stomach, compatible with a gastrointestinal stromal tumor with a low grade of malignancy.

patient survival; in all other cases they are malignant, and in a few cases they manifest as undifferentiated carcinomas with a high level of malignancy, always with a grim prognosis in the short term and capable of metastasizing everywhere. Neuroendocrine tumors can be sporadic or may have the characteristics of a familial disease. In about 80% of the cases tumors are non-functional[5,6].

Gastric carcinoids are particularly rare, representing only 3% of all neuroendocrine tumors of the gastrointestinal tract in dated reports[7,8]. More recent estimates indicate instead a frequency often greater than 10% of cases, and this may be explained by advances in instrumental and immunohistochemical diagnostic processes[9,10]. Gastric carcinoids are well differentiated in more than 90% of cases. A small minority of these tumors (1%) are located in the antral region and are characterized by cells which produce gastrin. In all other cases they are enterochromaffin-like (ECL) tumors. ECL cell tumors associated with hypergastrinemia are considered benign; in contrast, ECL cell tumors associated with normogastrinemia are considered relatively aggressive, associated with lymph nodes metastases in 55% of cases and hepatic metastases in 24% of cases.

Other hypergastrinemic tumors are associated with Zollinger Ellison syndrome: these are small sized multicenter tumors associated with dysplastic lesions localized on the gastric fundum, without atrophy of the oxyntic mucosa.

A small proportion of stomach carcinoids (6%) consist of barely differentiated tumors that show a negative prognosis in the short-term. They can occur in association with epithelial tumors of the stomach[11,12].

Of the cases described in the literature, the type 1 gastric carcinoid or ECL cell carcinoid is the most frequent, representing about 80% of cases[13]. These appear with a pattern of atrophic chronic gastritis and are associated with a marked hypergastrinemia. Patients diagnosed with these tumors are predominantly female (75%), with an average age equal or a little over 60 years, as in the case we present in the current article. These tumors are usually multiple and multicenter, with a size less than one centimeter (77% of cases), infiltrating the mucosa and submucosa in approximately one quarter of cases. Only rarely (1-2%) do these tumors reach a larger size and require resection. In all other cases these tumors are considered a disease with limited malignant potential and are therefore, as in the case we presented, subjected to pharmacological treatment with combination of somatostatin analogs and anti-H2 or inhibitor of the protonic pump, with the double objective of limiting the production of gastrin by neuroendocrine cells and controlling the secretion of chloridric acid[14]. For these reasons, as in the case described, as well as in the other cases observed by us of type 1 gastric carcinoids, it was not necessary to introduce a more extended radiological stage in the staging of the disease.

Cerebral tumors are also considered rare, accounting for about 2% of all malignant neoplasms in adults in the US. According to estimates provided by the American Cancer Society, every year in the US new diagnoses of cerebral and nervous system neoplasms account for more than 18,000 cases, with 12,000 deaths[15]. Data collected by the Central Brain Tumor Registry of the United States indicated an overall incidence of 18.16/100,000/years in 2004-2005[16]. The incidence of cerebral tumors is higher amongst males than it is in females (7.6 vs 5.4/100,000/year)[17], with a peak between 65 and 79 years. Various tumors of the central nervous system can be associated with rare genetic diseases, the most common of which is type 1 neurofibromatosis (NF1), autosomal dominant. Patients affected by this disease present a series of dermatological symptoms and are exposed to greater risk of optic gliomas and astrocytomas. In the case we observed, where a hypergastrinemic gastric carcinoid was associated with a grade IV glioblastoma multiforme[18], we were able to exclude the contemporaneity with a NF1. Furthermore, for the glioblastoma multiforme there is no evidence of tissue hyperexpression of

chromogranin A[19]. Therefore the association of these two low incidence tumors must be considered completely unusual, as in the case observed by us.

The Merkel cell tumor is a rare neoplasm of the skin, described first by Toker in 1972[20] as a skin trabecular carcinoma; subsequent histochemical research has created the term of neuroendocrine carcinoma of the skin, which is characterized by the presence of neurosecretory granules[21]. With a very low incidence (about a thousand cases have been described), the Merkel cell tumor involves mainly patients over 60 years old (79% of cases), with a greater incidence in females[22]. The most common area affected by the tumor is the skin of the head and neck, followed by the limbs, the trunk and the mucosas (10% of cases). The neoplasm is typically found as a single lump, raised or in a plaque, red-purple in color, with a smooth surface. Its size can vary, up to 15 cm in diameter, with an average diameter[22] of 3 cm. A high incidence of the disease has been highlighted amongst patients with recent transplants[23], and is more aggressive in this setting probably due to the immunodepressed status of the patient. The long-term prognosis is particularly severe in the advanced stages of the disease, with aggressive histological characteristics and very limited therapeutic scope[24]. Merkel cell tumor has frequently been described in association with squamous cell carcinoma of the skin, growing separately (in synchronism or metachronism) or in close contact[25]. In the former case the lesions are caused by a series of factors, the main one being exposure to sunlight. In the latter case, an origin from a common precursor is implicated. The association between Merkel and squamous carcinoma (synchronic or metachronic), present in about 34% of the cases[26] has been described in two transplant patients[27] and in one case also in association with a basal cell carcinoma. The case we observed, where a Merkel cell tumor and a squamous carcinoma coincide and exist on the same lesion, is the second such case reported[28]. The contemporaneous presence of the two lesions can be interpreted as a common answer by different cells to the same carcinomatous stimulus, such as a chronic exposure to sunlight, which supports the idea of a form of competition between Merkel and squamous carcinoma.

GISTs are a rare occurrence, though the most frequent amongst the mesenchymal tumors, with an approximate incidence of 11-15/100,000/year including autoptic cases (about 10% of all cases) and incidentalomas (about 20%). They are characterized by expression of the KIT protein and of CD34 and by mutations in the kit receptor tyrosine kinase gene[29-31]. GISTs are a morphologically heterogeneous tumor, with histotypes varying from spindle cells (70%) to epithelioid cells to mixed forms (10%). Rare variations include tumors characterized by myxoid stroma (5%), by paraganglioma-like aspects, by a carcinoid-like growth pattern, or by an evident pleomorphism (<2-3%). GISTs are in most cases sporadic (95%), though in some cases occur as part of the Carney triad, a rare syndrome of unknown etiology that affects predominantly young female patients and in which the GIST is associated with pulmonary chondroma and extra adrenal paraganglioma. In Carney syndrome, the GIST occurs prevalently on the gastric corpus and antrum, is generally multifocal and has a better prognosis compared to sporadic GIST[32]. In other cases GIST has been observed in association with NF1[33], and correlated to various neoplasms such as gastrointestinal carcinoma and somatostatinoma of the periampullary region. Another rare observation is the so called familial GIST syndrome[34-36] with which mastocitosis can be associated[37]. In some isolated cases the association with a MEN has been reported[38]. There is a known and significant preponderance in the male sex, with an average age at diagnosis of 55-65 years[29-31]. The most common signs of the disease are digestive hemorrhage, anemization and abdominal pain. Only 20% of GISTs are metastatic upon clinical presentation, affecting most frequently the liver and peritoneum. Many sporadic GISTs take the form of solitary lesions, most commonly in the stomach (60-70%), followed by the small intestine (30%) and more rarely the colon-rectum and esophagus (<5%).[29-31] About 75% of the kit mutations affect the iuxa membranosis domains (exon 11)[39-41]. A minority of GISTs, in particular those with a gastric localization and an epithelioid morphology, show the PDGFR mutation, most frequently in the tyrosine-kinase domain (exon 18)[41,42]. Some recommendations on the management of GISTs have recently been shared by a large work group[43].

Medullary thyroid carcinoma is a malignant neoplasm originating from parafollicular C cells, which themselves derive from the neural crest, and is a functional tumor that secretes the hormone calcitonin. This neoplasm represents about 5-10% of thyroid tumors and can occur in sporadic form (70-80% of the cases) or in familial

form within MEN 2, of which three different sub-types are known (MEN 2a, MEN 2b, familial medullary thyroid carcinoma)[44]. In addition, other rarer variations exist in association with skin lichen amyloidosis or with Hirschsprung disease[44]. The genetic defect responsible for MEN 2 involves germinal point mutations that activate the proto-oncogene RET that is localized in the centromeric region of chromosome 10. The survival rate after 10 years is 95% for cases where the disease is localized in the thyroid, and 55% for disease at the advanced lymph nodal or remote stage[45].

The yolk sac tumor of the testis is a teratoid germinal neoplasm, so called due to its capacity to selectively differentiate itself towards vitelline cells. Due to its rarity, there is no detailed epidemiological and clinical description of this neoplasm[46]. It is a very aggressive neoplasm, the natural history of which is based on the study of just a few case studies with low numbers of patients. The neoplasm is more frequent in males, with a bimodal distribution that peaks in the first four years of life and between the 2nd and 4th decade of life. This pattern suggests a primary role of sexual hormones as a cause of the tumor[47,48]. In testicular-derived forms, the rapid appearance of the tumor immediately after puberty could suggest the possibility of a neoplastic initiation of the cells during gestation, morphologically described as testicular dysgenesis[48-51]. About one quarter of yolk sac tumors are extra-gonadic, with this subset having a lower global survival (66.5%) in comparison with gonadic tumors both for females (81.4%) and males (89.4%)[52].

The association between the three neoplasms described for the third patient in this report, namely medullary thyroid carcinoma, yolk sac tumor and gastric GIST, has not been signaled in literature to date. Observations of GISTs (gastrointestinal, peritoneum and retroperitoneum) associated in synchrony with gastric and colon carcinoma, with ileal carcinoid, with pheochromocytoma, with anaplastic lymphoma and with disseminated squamous cell carcinoma[53] have been reported. The incidence of a second tumor associated with GIST ranges between 4.5% and 33% of the cases (mean 13%) and the gastric GIST itself is the most frequent localization (60%) when associated with other neoplasms[54]. In a series of 486 GISTs, the neoplasm was observed in synchrony or metachrony with gastrointestinal carcinoma (47%), lymphoma/leukemia (7%), prostatic carcinoma (9%), mammary carcinoma (7%), renal tumor (6%), pulmonary tumor (5%), female genital tract tumor (5%), bone and soft tissue tumor (3%) and malignant melanoma (2%)[54]. In particular, in 2.6% of the cases an association between GIST and a neuroendocrine tumor of the stomach (4 cases), of the pancreatic ampulla (4 cases), of the ileum (2 cases), of the small intestine (1 case), of the colon (1 case) and of the lung (1 case) was observed. The neuroendocrine tumor was an incidentaloma identified during a procedure to remove the GIST in 6 cases, while in 2 cases the diagnosis of the neuroendocrine tumor was made separately. Other metachronic cases included a pulmonary large cell neuroendocrine carcinoma and a medullary thyroid carcinoma. In 1% of the cases (6 patients) the association was between GISTs and seminomas, in each case in metachrony[54].

The clinical sequence of tumors in the case we describe in the current report involved first the medullary thyroid carcinoma followed by the testicular yolk sac then the gastric GIST. We cannot exclude that the GIST pre-existed the medullary thyroid carcinoma and remained undetected because it was asymptomatic. In fact, microscopic lesions of the icc hyperplasia type are known, as well as lesions of diameter <5 mm of the sclerosing stromal tumorlets type[54].

No relationship was found between GIST and NF1 nor between GIST and Carney syndrome in our case 3 patient. Furthermore, there is no evidence in the literature of the development of a GIST after radio or chemotherapy (in particular with PEB)[55]. The association between GIST and gonadic tumor raises the possibility of a link between seminoma and GIST, two neoplasms that are characterized by kit mutations, perhaps via a genetic predisposition of unknown mechanism. On the other hand, seminoma has never been reported amongst patients with a familial syndrome for GIST[34-37]. Basically, about 10% of GISTs develop in patients with other neoplasms, in synchrony or metachrony, and this phenomenon must be kept in consideration for the correct staging of the disease. A potential non-random association and a casual relationship between these neoplasms is yet to be studied and verified.

Whilst the association between gastric GIST and other malignant lesions of the stomach is quite common in the literature, reported in 11.5-25% of cases as synchronic and identified incidentally during gastric resection[56,57], the association between GIST and gastric carcinoid has

been reported in only 0.8% of cases[54]. These data are given without knowing, however, the original location of the GIST, although the gastric position is the most common site of GIST when associated to other neoplasms. In other cases, GIST was observed in association with a carcinoma of the colon-rectum (6.9%), with an in situ carcinoma of the stomach (2.3%), with a neuroendocrine tumor of the pancreas (2.3%)[58-60] and a double ileal localization of the carcinoid[61]. Furthermore it has been observed that GISTs accompanied by another neoplasm have a lower risk of aggression in comparison to those appearing singly[62]. The association of a GIST with a neuroendocrine tumor could imply a hypothetical role of c-kit in the development of the latter, the expression of which could be considered an early event of neoplastic transformation[63]. Most Merkel cell tumors express c-kit (>80%), and so do the bronchial neuroendocrine carcinomas (17-44%) and digestive neuroendocrine carcinomas (26%)[64]. This may have therapeutic implications regarding the use of targeted therapy with receptor-associated inhibitors such as imatinib[65] or other inhibitors of the tyrosine kinase[66].

Conclusions

Rare tumors offer us some interesting insights not only from the epidemiological point of view but also from genetic and biomolecular considerations, leading in recent years to effective therapeutic choices with the multitargeted molecules. The associations described in this report between several rare tumors, apart from representing a peculiarity, are also cause for speculation regarding potential geno-phenotypical mechanisms. The c-kit expression, typical of GISTs, but observed also in other epithelial and neuroendocrine tumors, not only broadens the possibility of acquiring new understanding of the carcinogenesis of these neoplasms, but also provides the possibility of as yet unknown roles for therapy with multitargeted molecules. The contemporaneous presence of other uncommon lesions, such as the Merkel cell tumor or the squamous cell carcinoma of the skin can be interpreted as a common response by the cell to the same mutagenic stimulus. In other cases, where a possible link is yet to be found to explain the synchronism or metachronism of low incidence neoplasms, random coincidence remains a possible explanation. However, we eagerly await for new instruments which could help us to demonstrate the possible relationships between low incidence neoplasms.

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