7. False positives and false negatives in neuroendocrine tumors diagnosis: clinical reports

Monika Ducceschi, Sara Pusceddu, and Marco Platania

Medical Oncology Unit 2, Centro di Riferimento per lo Studio e la Cura dei Carcinoidi e dei Tumori Neuroendocrini (CeRiCa), Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

ABSTRACT

Differential diagnosis NETs may be highly challenging. In order to exclude conditions that may mimic a neuroendocrine neoplasms, a deep knowledge of all the aspects of the disease, together with an adequate capacity to interpret clinical data and imaging findings and to put them in right correlation, are strongly warranted. Patients which suspected neuroendocrine neoplasms should be referred to reference centers to receive optimal multidisciplinary care. Free full text available at www.tumorionline.it

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP NETs) represent heterogeneous group of rare neoplasms that are often associated with vague and non specific symptoms, leading to a delayed diagnosis. Despite false negatives are common, the possibility of false positives diagnoses concretely exists. This eventuality depends in part on the poor knowledge of the disease, but the occurrence of several clinical conditions that could mimic a NET is also implicated.

Case 1

The patient Fifty-seven year old heavy smoker female in good general conditions. Familiar history was negative for neoplastic disease. Recent diagnosis of hypertension with symptomatic hypertensive crises due to the presence of epistaxis. The woman is as healthcare worker in assisted-living facilities. She has noted fatigue and weight loss over the last few months. Following the recommendation of her general practitioner, she had a chest X-ray in two projections which revealed the presence of a solitary pulmonary nodule of about 2.0 cm in size in the left apical region. This finding was absent in the previous chest radiogram which had been taken three years earlier.

Physical examination The patient was in good general conditions. Vesicular murmur was ubiquitously reduced. No other relevant semielogic alteration was found. Poor blood pressure control was confirmed and required the intensification of antihypertensive therapy.

Laboratory examinations and instrumental investigations After the admission to our Department, the patient started her diagnostic work-up in accordance with the applicable international guidelines for the diagnosis of pulmonary nodule of undetermined nature. Total body CT scans confirmed the presence of a solitary pulmonary nodule with irregular shape and spiculated margins, which was surrounded by aerated lung tissue without associated pleural effusion or atelectasis. TC scans excluded the presence of lymphadenopathy or distant metastases (Figure 1). Biochemistry revealed only an increase in the erythrocyte sedimentation rate (ERS >80 mm/1h; normal rate, 0-20 mm/1h by the Westergreen’s method). PET scans and carcinoembry-
oncic antigen (CEA), CA 19.9, CA 15.3 and CA 125 were all negative.

In consideration of the frankly malignant features of the lesion, additional investigations were performed in order to exclude primitive or secondary oncologic complications. Bronchoscopy, mammography, colonscopy, ENT and gynaecological assessments were negative as well.

Given the negative results shown by PET imaging and tumor marker determination and the lack of signs and symptoms suggestive of ongoing disease evolution, the patient was candidate for laboratory instrumental and clinical follow-up, and she was asked to return to our Institution within 60 days to perform a pneumologic visit and another whole body TC. Upon discharge from our Institution, the patient, following the advice of an acquaintance, referred to a thoracic surgeon for a specialist consult. After having taken into account the patient’s positive anamnesis for hypertensive crises and the finding of a PET-negative nodule, the surgeon recommended to perform chromogranin A (CgA) determination and Octreoscan® imaging to confirm or exclude the suspect of lung carcinoid associated with Cushing’s syndrome.

CgA determination revealed borderline values of 130ng/nL, but Octreoscan® showed an intense uptake corresponding to the known pulmonary lesion (Figure 2).

**Diagnostic conclusions** Suspected lung carcinoid associated with Cushing’s syndrome

**Therapy and clinical iter** In view of these findings, the patient was candidate to segmentectomy of the upper left division and locoregional lymphadenectomy. Intraoperative macroscopic examination showed an anthracotic lung parenchyma characterized by the presence of multiple, poltaceous nodules, the greatest of which measured about 2.5 cm in diameter. At microscopic examination panlobular emphysema and coalescent granulomas with central necrosis were detected. The intermediate wall exhibited epithelioid cells surrounded by fibroblasts, lymphocytes and polinucleated giant cells with nuclei which formed a palisade-like arrangement. No evidence of acid-fast bacilli was found. Lymph nodes were antracotic, and neoplastic formations were absent. These finding were consistent with the diagnosis of secondary pulmonary tuberculosis (TB). Therefore, the management of the case was put into the hands of the Villa Marelli regional TB reference center, where the patient underwent Mantoux intradermoreaction to tuberculin which tested negative all the times. Other investigations aimed at identifying the mycobacterium were negative as well. Currently the patient is asymptomatic, enjoys excellent general conditions, and undergoes regular check-ups at the reference TB center.

**Discussion** Neuroendocrine tumors (NETs) of the bronchopulmonary system account for approximately 30% of neoplasms of endocrine origin and are extreme-
ly heterogeneous for histopathologic, clinical and behavioral features. The estimated incidence of lung NETs is of 1.57/100,000/year and, although in the past 30 years a considerable increase in their frequency (6%/per years) has been referred, they represent only 2% of all lung neoplasms. According to the World Health Organization (WHO) of 2004, lung NETs can be subdivided into four distinct categories: typical carcinoids, atypical carcinoids, large cell neuroendocrine carcinomas and small cell neuroendocrine carcinomas. The majority of patients affected by bronchial carcinoid are asymptomatic at diagnosis; when symptoms are present, they include most frequently cough, hemoptysis, pneumonia, chest pain, dyspnea. Only 3-5% of pulmonary carcinoids are associated with hormone-related syndromes. These syndromes occur generally in presence of large tumor masses and/or hepatic involvement. Cushing’s syndrome is a hormonal disorder caused by ectopic hypersecretion of adrenocorticotropic hormone (ACTH). It is detectable in only 2% of bronchial carcinoids and is typically associated with the most aggressive histotypes. Conversely, only 1% of patients who develop Cushing’s syndrome harbour a carcinoid of the lung. In the last years, clinicians have demonstrated a renewed interest in NETs. Indeed, this situation has contributed to improve the diagnosis of NETs, but it has also led to an increase in the number of misdiagnosed cases. In light of these considerations, the diagnostic iter of patients highly suspected to harbour a neuroendocrine pathology should comprise the determination of circulating endocrine markers followed, in case of positivity of such markers, by Octreoscan® imaging. However, both marker determination and Octreoscan® have not absolute specificity, and there are several conditions which may lead to false-positive or false-negative findings. Indeed, the presence of abnormal values of CgA is one of the main factors which may lead clinicians to misleading interpretations. CgA values, in fact, may be deceptively altered by several situations unassociated with neuroendocrine disease, including the use of medications such as proton pump inhibitors, and clinical conditions such as chronic atriope gastritis, renal failure, hepatic failure and inflammatory bowel diseases. Octreoscan® is a fundamental tool in the diagnostic and therapeutic management of NET patients. Its specificity varies from 50% to 100% and is strongly influenced by the technique used as well as by the institution in which the exam is performed. False-positives have a frequency of 12% and may result from the accumulation of radiotracer in normal structures (pituitary, thyroid, liver, spleen, kidneys, bowel, gallbladder, ureters, bladder), but also from the presence of non neuroendocrine neoplastic pathologies, including lymphomas or inflammatory, autoimmune and infectious diseases (Crohn’s disease, ulcerative rectocolitis, rheumatoid arthritis, sarcoidosis and other granulomatous diseases, tuberculosis and aspergillosis). Specifically, in granulomatous diseases hyperfixation is explained by the presence of activated monocytes which selectively express somatostatin receptor subtype 2A. The clinical case discussed herein highlights some important critical points, including the inadequacy of the anamnestic investigation and the mistaken interpretation of both signs and symptoms and diagnostic tests. In particular, we did not considered that the patient, being an healthcare worker in assisted-living facilities, had come into contact with an index case of tuberculosis. This missed observation led us to underestimate the possible correlation of the pulmonary lesion with infectious causes, and, most importantly, to omit the Manteaux test in a time of high recrudescence of this pathology in our country. Moreover, hypertensive crises were regarded as a possible manifestation of a paraneoplastic Cushing’s syndrome. Finally, the minimal elevations of CgA levels, which were due to hypertension, were regarded as pathognomonic of endocrinopathy based on Octreoscan® positivity.

Case 2: Neuroendocrine carcinoma of the pancreas: hypoglycemic syndrome and insulinoma

The patient Seventy-six year old, non-smoker female in good general health conditions (Performance Status according to the Eastern Cooperative Oncology Group criteria: 0). The remote pathological anamnnesis was positive for high blood pressure. Thoraco-abdominal physical examinations revealed no anormalities.

Laboratory examinations, instrumental investigations and therapy From January 2008, following the onset of dyspepsia, abdominal pains and nausea, the patient underwent a series of tests which revealed multiple hepatic nodules suggestive of secondary lesions. Computed tomography (CT) confirmed the presence of multiple, roundish coarse lesions in both hepatic lobes. The nodular lesions were characterized by dyshomogeneous arterial phase enhancement and appeared dyshomogeneously hypodense during the portal phase. The largest nodules were located in the VIII, VI, and IV segments of the liver and measured 48 mm, 60 mm and 40 mm in their greatest dimension, respectively. Impairment of the portal vein flow was observed. An expansive lesion displaying in part a polycyclic morphology and dyshomogeneous density was also detected. It measured 55 mm in the largest transverse diameter, was undistinguishable from the pancreatic body-tail and was “uncleavable” by dislocated splenic vessels. Ultrasound-guided needle biopsy was performed on a focal hepatic lesion for histological typization, which confirmed the presence of malignant epithelial cells with morphological features consistent with the diagnosis of poorly differentiated adenocarcinoma. Mucinic tumor...
markers CA 19.9 and CA 125 showed levels of 42 UI/ml and 68 UI/ml, respectively. The patient received first-line chemotherapy with gemcitabine for a maximum of 12 cycles, which resulted in the radiological, biochemical and objective stabilization of disease. At this point, the woman was sent to follow-up. In the August 2009, during a scheduled follow-up visit, CT scans of the encephalon, chest and abdomen confirmed disease stabilization, whereas the values of serum CA 19.9 were slightly above the normal range. In consideration of the indolent course of the disease, as well as of the non significant values of the mucinic marker CA 19.9, the examination of the histologic preparations obtained from the biopsy previously performed in another center, together with the determination of CgA levels, were required at out Institution. Some weeks later, when the patient returned to our Institution for the scheduled appointment, she presented to us with a flashy bandage of the left upper limb and swelling in the left hemiface. She referred a fracture at the neck of Humerus after incidental fall caused by an episode of disorientation/confusion. In effect, similar episodes had already occurred over the last six months, but they had remained unref- erred. Blood chemistry documented a pronounced hypoglycaemia (the most recent values of blood glucose were of 22 mg/dl) and CgA levels >7000 ng/mL, whereas the examination of the histologic preparations confirmed the diagnosis of suspected hepatic metastases from poorly differentiated carcinoma, which had been posed in another center. Based on the high values of CgA and on the evidence of hypoglycaemia inducing neurological symptoms, the patient was admitted to out Department in order to keep blood sugar levels under control and to perform another histologic typization, in the attempt to confirm or exclude the suspect of neuroendocrine disease. During hospitalization a more accurate anamnesis was collected, and it was found that the occurrence of symptoms related to fasting hyperglycemia had started about 6 years before. Specifically, these symptoms included asthenia and drowsiness, and their management required the intake of sugar or glucose. Accordingly, the woman had changed her dietary habits by increasing the frequency of meals, which resulted in a weight gain of about 10 kg. At the time of hospital admission, glycemic values were 22 mg/dL and they returned to the normal range after intravenous administration of glucose solution. The other hematochemistry tests fell within the normal limits, but chest X-ray documented a light interstitial thickening throughout both lungs. Echocardiographic examination revealed a moderate mitral regurgitation together with a mild left atrial enlargement. The study of the general hormonal profile showed subclinical hypothyroidism (thyrotropin-stimulating hormone [TSH], 7 mU/L) but normal adrenocortical function. These findings excluded the presence of hypoglycemia due to adrenal insufficiency. The glucose/insulin ratio was then calculated at different hours of the day, showing an abnormal secretion of the hormone in presence of glycemic values well below the normal range, which led to a suspected diagnosis of insulinoma. Abdominal TC scans obtained with the use of contrast agent confirmed the presence of a nodular lesion of about 60 mm in diameter in the pancreatic tail. Octreoscan® revealed several areas of strong uptake expressing high levels of somatostatin receptors subtypes 2 and 5, which were ubiquitously distributed in the liver and in the pancreatic tail region. The patient underwent another hepatic biopsy which supported the diagnosis of well differentiated neuroendocrine carcinoma, probably of pancreatic origin (MIB-1: <1%), consistently with the presence of metastases from malignant insulinoma.

**Diagnostic conclusions** Functioning neuroendocrine carcinoma of the pancreas, consistent with the diagnosis of well differentiated insulinoma with low metastatic proliferative index at hepatic level.

**Therapy and clinical course** In consideration of the histologic characteristics of the disease, the receptor immunopositivity for 111Indium–pentetreotide and the presence of hypoglycemic syndrome in its typical form, and since the patient was not amenable to surgery because of the advanced age, obesity and the extension of disease, she was candidate for systemic hormonotherapy with somatostatin analogs. Initial treatment consisted of octreotide 0.1 mg 3 times per day, which was subsequently replaced by the long-acting release (LAR) formulation (30 mg every 28 days) plus diazoxide 5mg/kg die. This therapy reduced the frequency and severity of hypoglycemic attacks. From the September 2009 on, no other severe hypoglycemic episode has been referred. The success of octreotide treatment may be explained by the age-related decline in metabolism, and may be considered a possibly valuable option for elderly patients diagnosed with insulinoma, particularly those who are judged not amenable to surgery and chemotherapy.

**Case 3: Munchausen Syndrome simulating a neuroendocrine tumor (NET)**

We report a case of Munchausen syndrome (MS) simulating a NET. This rare psychiatric disorder was first described by Richard Asher. Subjects affected by this disorder exaggerates or creates symptoms of illnesses in themselves in order to gain investigation, treatment, attention, sympathy, and comfort from medical personnel. The female patient we describe herein was admitted to our hospital because she was complaining of symptoms similar to that reported in the carcinoid syndrome. The inconsistencies between the referred signs and the results of the radiological investigation prompt-
ed clinicians to suspect she was simulating. An extensive history of multiple prior admissions to several hospitals was indicative of MS and the psychiatric consultant agreed with the above diagnoses. So, to avoid expensive medical procedures and unnecessary medical interventions, we generally alert physicians about rare cases in which suspected NET tumors really mask a MS.

**Case report** A 54-year-old female nurse was admitted to our hospital complaining of symptoms of post-prandial diarrhea (more than 5 episodes daily), sudden flushing and profuse sweating, abdominal pain and bronchospasm. Upon hospital admission she was evaluated for serum CgA and urinary 5-hydroxyindoleacetic acid (5-HIAA). CgA was 80 ng/mL (normal range, 19-98), while 5-HIAA resulted increased to 11.8 mg/24 hour (normal range, 0.7-8.2). According to the patient, she was affected by a NET tumor presenting with a classical carcinoid syndrome. Surprisingly, she was highly knowledgeable about this rare disorder, and after having listened to her description of symptomatology the admitting physician was concerned that she could be really affected by a NET tumor. After the admission to the hospital, routine examinations were performed and revealed a normal electrocardiogram and chest radiograph. Blood tests were apparently within the normal ranges as well. At physical examination, overweight was evident but nothing else seemed to deserve particular medical attention. A total body computed tomography (CT) scan was performed showing a single liver cyst not more than 1 cm in longer diameter. In the meantime, the woman continued to complain of worsening symptoms, including an increased frequency of diarrhea episodes and abdominal pain attacks. Therefore, since conventional methods are inadequate to detect smaller carcinoids, an octreoscan scintigraphy was performed. However, also this study confirmed the absence of metastasis or other site of occult disease. The hypothesis that the patient was inventing her symptoms became more consistent when, in spite of our nutrition recommendation to avoid foods which could be able to alter the 5-HIAA urinary test, the oncologist fellow found chocolate tables in her bedside table. At this point, it became suddenly clear why the woman referred flushing when anybody could note it and also because “the imaginary diarrhea” did not cause weight loss or electrolyte abnormalities. When medical records from prior hospitalizations were obtained, an extensive history of previous admissions for complaints resembling those she reported to us was documented. The psychiatric consultant finally indicated that the patient was affected by the Munchausen Syndrome and that she was inducing her symptoms in order to prolong hospitalization and perform new investigations. After discharge from the community hospital, she refused all psychiatric services and did not present herself at the scheduled outpatient appointment.

**Discussion** Although their incidence has more than tripled over the last 30 years in the US, NET tumors account for 0.7% of all malignancies. Gastroenteropancreatic neuroendocrine tumors (GEP-NET) arising from the gastrointestinal tract represent the majority (70-85%) of NETs, but they can occur also in several others body districts. NETs form a group of rare and heterogeneous neoplasms, and the clinicians’ awareness of this complex disease it still too low. At an early stage they are characterized by the presence of unspecific signs and vague symptoms which lead frequently to delayed diagnosis. An high grade of suspicion is required to detect these tumors and false negatives are common. On the other hand, clinicians must be aware that other different morbidities may mimic a NET. The case we have just described is of particular interest because it deals with a rare psychiatric disorder, known as Munchausen Syndrome (MS), which often mislead doctors. Specifically, MS is a type of factitious disorder in which the affected subject acts as if he or she has an illness by deliberately producing, feigning, or exaggerating symptoms with the only aim of draw attention or sympathy to himself or herself. The syndrome was named after Baron Munchausen, a German officer who lived in the 18th century and was known for embellishing the stories of his life and experiences. This condition who was first described in 1951 by Richard Asher, and is different from hypochondriasis in which affected people believe to have a disease.

Patients presenting with Munchausen’s Syndrome are highly knowledgeable on the practice of medicine, and are able to produce symptoms or alter diagnostic tests to assume the role of “patient”.

In our case, the patient simulated a carcinoid by describing and complaining of symptoms similar to those observed in the typical carcinoid syndrome. To this regard, it should be highlighted that the classical carcinoid syndrome, which is characterized by flushing, sweating, diarrhea, abdominal pain, bronchospasm and right-sided heart failure, is a fairly infrequent event occurring in less than 10% of NET cases at the time of diagnosis. Moreover, depending on the tumor’s release of bioactive substances into systemic circulation, it is improbable to observe classical syndrome features when radiological examinations (US abdomen or CT scan) result negative for massive liver metastatization. In conclusion, our case emphasizes the importance of making a differential diagnosis to proceed in the expensive NET work-up. In some cases, as in that described herein, the patient reliability in reporting symptoms should be carefully considered.

**References**


