

Sarcoidosis mimicking metastatic progression of pancreatic neuroendocrine tumor

A case report

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Abstract

Rationale: Pancreatic neuroendocrine tumors (PNETs) account for less than 5% of all pancreatic tumors. PNETs develop from pancreatic endocrine islet cells and have a variable range of malignant potential. These neoplasms tend to have a slower growth rate than exocrine tumors and may remain undetectable for years. Achieving a correct diagnosis and staging is of key importance for the optimal management of the disease and requires experience with the disease, an accurate clinical status evaluation and a critical interpretation of the radiological findings derived from morphological and functional imaging techniques as well as an integrated multidisciplinary approach. The possibility that some clinical data and radiological findings encountered during the diagnostic and staging procedures may not be related to PNETs but to concomitant clinical conditions should always be taken into consideration. This is mandatory as an incorrect stadiation may lead to patients' mis-management.

Patient concerns: We report the case of a 34-year-old female, with a past medical history of idiopathic acute pancreatitis, presenting with a severe upper abdominal pain, steady and radiating to the back.

Diagnoses: Initial investigations incidentally detected a nonfunctioning pancreatic neuroendocrine tumor (NF-PNET) of intermediate grade G2. Subsequent investigations aimed at determining a correct tumor staging showed a negative indium-111-OctreoScan but an increased 18F-labeled fluorodesoxyglucose (18F-FDG) uptake in multiple bilateral nodules in the lungs and in 1 nodular lesion located in the right gluteal subcutaneous tissue. An early tumor progression of a G2 NF-PNET that had to be treated with chemotherapy was suspected.

Interventions: The histological examination of the gluteal subcutaneous nodule showed noncaseating granulomas, disproving the initial clinical suspect and allowing the diagnosis of active sarcoidosis in the G2 NF-PNET patient.

Lessons: A misdiagnosis and a consequent therapeutic mismanagement were avoided with the support of an integrated multidisciplinary team.

Abbreviations: 18F-FDG = 18F-labeled fluorodesoxyglucose, ACE = angiotensin-converting enzyme, F-PNETs = functioning pancreatic neuroendocrine tumor, IPMT = intraductal papillary mucinous neoplasm, MRCP = magnetic resonance cholangiopancreatography, NET = neuroendocrine tumor, NF-PNET = nonfunctioning pancreatic neuroendocrine tumor, OctreoScan = Indium-111-Octreotide Scintigraphy scan, PET/CT = combined positron emission tomography/computed tomography scan, PNEC = pancreatic neuroendocrine carcinoma, PNET = pancreatic neuroendocrine tumor, PTLB = CT-guided percutaneous transthoracic lung biopsy, SUV_{max} = maximum standardized uptake value, WHO = World Health Organization.

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1. Introduction

Pancreatic neuroendocrine tumors (PNETs) are a rare heterogeneous group of neoplasms differentiated as either functioning (F-PNETs) or nonfunctioning (NF-PNETs), depending on their ability to secrete biologically active hormones. PNETs exhibit a variable range of malignant potential.^[1] The current World Health Organization (WHO) classification of PNETs is based on the combination of morphological features and proliferation grading system (G), assessed by the Ki-67 index: well-differentiated PNET G1 (Ki-67 index ≤ 2%) and PNET G2 (Ki-67 index: 3–20%) and poorly differentiated pancreatic neuroendocrine carcinoma PNEC G3 (Ki-67 >20%). Most G1 and G2 PNETs are slow-growing tumors, whereas G3 PNECs may quickly progress to an unresectable metastatic disease.^[2] Staging of PNETs requires OctreoScan, integrated, in selected cases, with an 18F-FDG combined positron emission tomography/computed tomography scan (18F-FDG-PET/TC).^[3] Indium-111-Octreotide Scintigraphy scan (OctreoScan) identifies tumors by radiolabeled targeting of somatostatin receptors, whereas 18F-FDG-PET/TC scan measures the differential

tissue glucose transport. In general, well-differentiated G1 or G2 PNETs are OctreoScan positive and 18F-FDG-PET/TC scan negative, whereas the opposite is true for poorly differentiated G3 PNETs. In G1 and G2 PNETs, 18F-FDG-PET/TC scan should be carefully considered in the case of Octreoscan negativity.

Sarcoidosis is a systemic inflammatory disease associated with an abnormal immune response characterized by the development of noncaseating epithelioid granulomas in the tissues. The disease most commonly involves lungs, skin, and eyes and rarely causes severe symptoms and/or functional impairment. The clinical course of sarcoidosis is extremely variable. Spontaneous remission occurs in about two-thirds of patients, whereas the clinical course is chronic or progressive in 10% to 30% of patients.^[4] Recently, 18F-FDG-PET/CT scan has been demonstrated to be a sensitive and reliable tool to assess inflammatory activity and disease extent.^[5]

2. Presenting concerns

A 34-year-old female was admitted to the hospital due to severe upper abdominal pain, steady and radiating to the back.

3. Clinical findings

Her past medical history was unremarkable except for an idiopathic acute pancreatitis managed conservatively 2 years earlier. On examination, the abdomen was distended with a mild tenderness in epigastrium.

4. Diagnostic focus and assessment

Laboratory tests were unremarkable, including pancreatic enzymes levels. An abdominal ultrasound scan revealed a large heterogeneous cystic lesion located in the upper abdomen, in the pancreatic tail region. A magnetic resonance cholangiopancreatography (MRCP) showed absence of intra and extrahepatic bile duct dilatation, a gallbladder with normal walls containing biliary sludge, a Wirsung duct with a regular course along the pancreatic head and body and a cystic lesion, 6 cm in diameter, located in the pancreatic tail with no clear communication with the main pancreatic duct. Parenchymal signs of chronic pancreatitis were present. A mixed type intraductal papillary mucinous neoplasm (IPMT) of the pancreas was suspected (Fig. 1).

5. Therapeutic focus and assessment

The patient was referred to the surgical department for intervention. The operative findings showed a 6 × 6 cm cystic mass, tightly connected to the pancreatic tail. A cholecystectomy and a distal spleno-pancreatectomy were performed. Histology revealed the absence of splenic alterations, a gallbladder containing biliary sludge, a voluminous body/tail pancreatic pseudocyst with hemorrhagic content and a coexistent, incidentally discovered, neoplasia, 2.2 cm in diameter, infiltrating the pancreatic parenchyma. The tumor cells displayed an organoid architecture with nesting and trabecular pattern and absence of vascular invasion. Immunohistochemically, the tumor cells were positive for epithelial cytokeratins AE1/AE3 and synaptophysin, and negative for vimentin, chromogranin A, and nuclear β -catenin, consistent with a diagnosis of moderately differentiated (intermediate grade G2) pancreatic neuroendocrine tumor (G2-PNET). The Ki-67 proliferative index was 15%.

6. Follow-up and outcomes

Based on the finding of a G2-PNET, further diagnostic investigations were scheduled. Laboratory tests showed normal serum chromogranin A, gastrin, neuron-specific enolase, and urinary 5-hydroxyindoleacetic acid levels. The glycemic profile and the bowel habit were normal and the patient did not present any symptom which could be compatible with carcinoid syndrome; therefore, no further additional laboratory tests were requested. A whole body functional imaging study with OctreoScan was performed, in order to identify unknown metastatic sites and to gain information on the functional expression of somatostatin receptors. The OctreoScan resulted negative for focal radionuclide tracer uptake in the body. For a correct staging, OctreoScan outcome triggered the decision to perform a combined positron emission tomography/computed tomography scan (18F-FDG-PET/CT). The exam showed increased 18F-FDG activity in the apical region of the right upper lobe of the lung and in multiple other bilateral pulmonary parenchymal foci, at least 6, coinciding with nodules detected on co-registration CT. The maximum standardized uptake value (SUV_{max}) of the nodular lesion in the apical right lung lobe was 7.9 and ranged from 2.2 to 6.5 in the other pulmonary parenchymal foci. Furthermore, a clear area of increased 18F-FDG uptake was detected in the subcutaneous tissue of the right

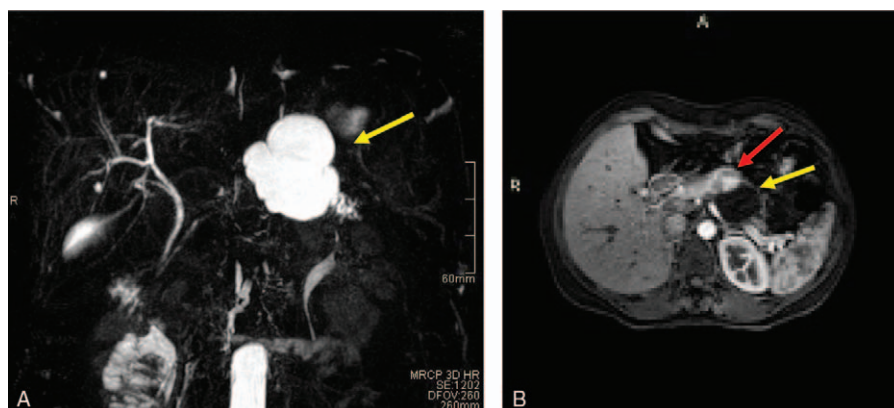


Figure 1. Magnetic resonance cholangiopancreatography (MRCP): (A) body/tail pancreatic pseudocyst. (B) pseudocyst (yellow arrow), neuroendocrine tumor (red arrow). MRCP = magnetic resonance cholangiopancreatography.

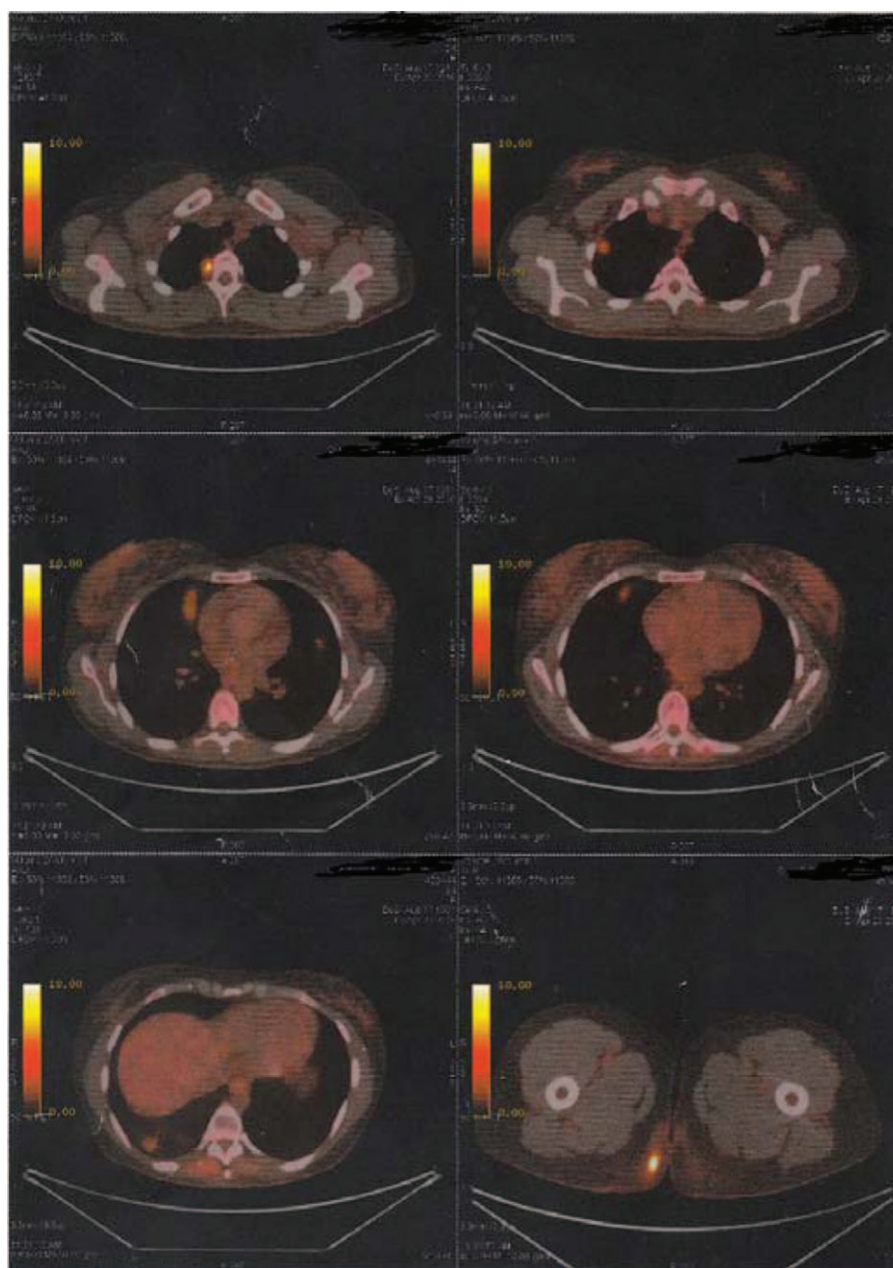


Figure 2. 18F-FDG-PET: multiple pulmonary parenchymal nodular lesions and area of increased 18F-FDG uptake in the right gluteal subcutaneous tissue (lower-right image).

gluteus (SUV_{max} 14.4) (Fig. 2). The nodular lesions were highly suspected for metastases and a treatment with chemotherapy was considered. Following multidisciplinary neuroendocrine tumor (NET) board discussion, a CT-guided percutaneous transthoracic lung biopsy (PTLB) was recommended, in order to define the exact nature of pulmonary nodules. The preliminary CT scan showed a definite fading of the lung nodules in comparison with the previous imaging; therefore, the biopsy was not performed (Fig. 3). This event was considered peculiar as the patient had not received any treatment except for steroids as premedication for iodinate intravenous contrast agents. Therefore, the nodules could not be attributed to PNET metastasis, as such a dramatic improvement at short-term investigations, under no specific treatment, would be not compatible with a malignant nature of

the lesions. The tumor board recommended a biopsy of the subcutaneous gluteal nodule.

The histological specimen of the nodular lesion, 2 × 2 cm in diameter, constituted of mild dermal fibrosis and a dense lymphoplasmacytic infiltrate with few neutrophils, surrounding multiple foci of noncaseating epithelioid cell granulomas, was consistent with a diagnosis of sarcoidosis (Fig. 4). On further examination, an ophthalmologic assessment revealed a paucisymptomatic anterior uveitis and laboratory results showed an increased serum angiotensin-converting enzyme (ACE) level (114.8 U/L; reference range 8.0–52.0 U/L). A definitive diagnosis of G2-PNET and concomitant active sarcoidosis was made. The patient was started on oral corticosteroids and a regular follow-up was scheduled. A subsequent thorax CT scan, performed following



Figure 3. Computed tomography (CT): Fading of the nodule in the right lung base. CT=computed tomography.

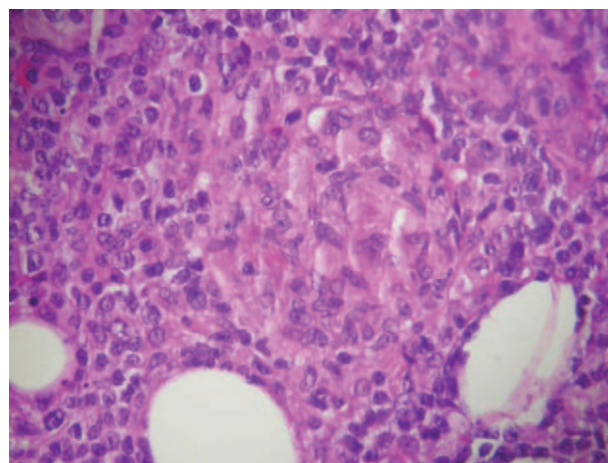


Figure 4. Hematoxylin and eosin (H&E) stain: noncaseating epithelioid cell granuloma. H&E=hematoxylin and eosin.

a 3-month corticosteroid course, showed a further fading of the lesions, providing further confirmation of the benign, steroid-sensitive nature of the lung nodules, compatible with sarcoidosis. A timeline of the clinical case reported is shown in Table 1. The patient gave informed consent for clinical case publication and our institute Research Department approved the study.

7. Discussion

The case reported is unusual because a combined 18F-FDG-PET/TC scan, performed for staging of an OctreoScan negative G2-PNET, showed multiple nodular lesions in the lung and in the right gluteal subcutaneous tissue highly suspected for a metastatic progression of the disease. The histological examination of the subcutaneous nodule biopsy disproved the clinical suspect and allowed to diagnose the unexpected and unsuspected simultaneous presence of an active sarcoidosis.

An association between sarcoidosis and malignancy, mainly hematological, including Hodgkin and non-Hodgkin lymphoma, has been described in several studies.^[6,7] The association with solid tumors has been reported less frequently.^[8] To explain the increased malignancy risk in sarcoidosis patients, it has been hypothesized that the abnormal immune system response and the

chronic tissue inflammation related to sarcoidosis could trigger the development of cancer.^[9]

The association between sarcoidosis and pancreatic malignancy, particularly of neuroendocrine origin, has been rarely reported.^[10]

The accuracy in the differentiation between malignant dissemination of tumors and benign diffuse granulomatous disease such as sarcoidosis is affected by the limitations of the available imaging techniques. Most NETs metastases are hypervascular, similarly to the primary neoplasm, visualized as hyperattenuating, enhancing masses after the administration of intravenous contrast, with or without central necrosis.^[11,12] Liver metastases of NETs are the most common, whereas pulmonary, pleural, and mediastinal metastatic disease are less common, except for thymic NETs.^[13] The average sensitivity of CT scan in the diagnosis of primary NETs is 73%, whereas the sensitivity for metastases is 80% for hepatic metastases and 75% for extrahepatic metastases.^[14,15] The sensitivity of CT scan in the diagnosis of pulmonary sarcoidosis is 78%.^[16]

The sensitivity of 18F-FDG-PET/CT scan in the stadiation of tumors is high; however, it has been shown to be nonspecific, with a false positive rate as high as 13%.^[17] Multiple reports described the possibility of false positive 18F-FDG-PET/CT scan in neoplastic patients, due to clinical conditions other than tumors, including acute and chronic inflammatory condi-

Table 1

Case report timeline.

Complaint/investigations	Details
Presenting symptoms	Severe upper abdominal pain, radiating to the back
First investigations	Pancreatic cystic lesion (diameter 6 cm), suspect of IPMT
Abdominal ultrasound	
MRCP	
Surgical intervention: distal splenopancreatectomy and cholecystectomy	Histology: hemorrhagic pancreatic pseudocyst, incidental moderately differentiated intermediate grade G2-PNET
OctreoScan	Negative
PET/CT	Multiple bilateral panchymal nodules + subcutaneous gluteal nodule
Multidisciplinary NET board discussion	
CT-guided percutaneous transthoracic lung biopsy	Not performed due to fading of the lung nodules
Subcutaneous gluteal nodule biopsy	Histology: sarcoidosis

CT=computed tomography, IPMT=intraductal papillary mucinous neoplasm, MRCP=magnetic resonance cholangiopancreatography, NET=neuroendocrine tumor, OctreoScan=Indium-111-Octreotide Scintigraphy scan, PET/CT=combined positron emission tomography/computed tomography scan, PNET=pancreatic neuroendocrine tumor.

tions.^[18,19] Active granulomatous conditions, such as sarcoidosis and tuberculosis, result in accumulation of 18F-FDG and the intensity of uptake reflects disease activity.^[20–23]

Physicians' ability to differentiate between sarcoidosis and malignancy is important because this event, if not acknowledged, may be the cause of misdiagnosis, incorrect staging, and consequent therapeutic mismanagement. In fact, in the case reported, a rapid progression of a G2 NF-PNET was initially suspected and a treatment with chemotherapy was considered.

PNETs are heterogeneous neoplasms from a clinical and biological point of view.

In order to make a correct diagnosis and staging, physicians require experience with the disease, an accurate clinical status evaluation, and a critical interpretation of the radiological findings derived from morphological and functional imaging techniques.

The possibility that some clinical data and radiological findings encountered during the diagnostic and staging procedures may not be related to PNETs, but to concomitant, clinical conditions should be taken into account in the differential diagnosis.

A report from a tertiary Italian tumor center described 8 cases referred for pathological assessment of NETs diagnosed in other centers, in which, following subsequent investigations, the diagnosis of NETs was disproved. Among these, 1 patient, referred with a suspect of primary lung tumor, was in fact diagnosed with lung sarcoidosis.^[24]

The key knowledge of this paper include the report of the association of 2 relatively rare conditions with overlapping clinical manifestations and the acknowledgement that an integrated and proactive multidisciplinary team management is a crucial factor to avoid clinical errors.

The application of the present report in clinical practice is to keep a critical approach to the interpretation of clinical data, with an open-minded attitude and possible stop-the-line decisions in case of uncertainty, in order to promote patients safety. Moreover, in the light of the experience gained in this work, we would like to encourage a routine integrated multidisciplinary team management, as this is documented to guarantee the optimization of care of neoplastic patients, particularly in the case of PNETs, due to their heterogeneity and clinical complexity.

References

- Halfdanarson TR, Rabe KG, Rubin J, et al. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol* 2008;19:1727–33.
- Klimstra DS. Pathology reporting of neuroendocrine tumors: essential elements for accurate diagnosis, classification, and staging. *Semin Oncol* 2013;40:23–36.
- Squires MH3rd, Volkan Adsay N, Schuster DM, et al. Octreoscan versus FDG-PET for neuroendocrine tumor staging: a biological approach. *Ann Surg Oncol* 2015;22:2295–301.
- Iannuzzi M, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. *JAMA* 2011;305:391–9.
- Mostard RL, van Kroonenburgh MJ, Drent M. The role of the PET scan in the management of sarcoidosis. *Curr Opin Pulm Med* 2013;19:538–44.
- Simsek S, van Leuven F, Bronsveld W, et al. Unusual association of Hodgkin's disease and sarcoidosis. *Neth J Med* 2002;60:438–40.
- Brincker H. The sarcoidosis-lymphoma syndrome. *Br J Cancer* 1986;54:467–73.
- Kim JJ, Park JK, Wang YP, et al. Lung cancer associated with sarcoidosis—a case report. *Korean J Thorac Cardiovasc Surg* 2011;44:301–3.
- Asklung J, Grunewald J, Eklund A, et al. Increased risk for cancer following sarcoidosis. *Am J Respir Crit Care Med* 1999;160:1668–72.
- Mastroberto M, Berardi S, Fraticelli L, et al. Sarcoidosis and sarcoid-like reaction associated with pancreatic malignancy: are you able to read a riddle? *JOP* 2012;13:454–7.
- Reznek RH. CT/MRI of neuroendocrine tumours. *Cancer Imaging* 2006;6:S163–77.
- Bader TR, Semelka RC, Chiu VC, et al. MRI of carcinoid tumors: spectrum of appearances in the gastrointestinal tract and liver. *J Magn Reson Imaging* 2001;14:261–9.
- Scarsbrook AF, Ganeshan A, Statham J, et al. Anatomic and functional imaging of metastatic carcinoid tumors. *Radiographics* 2007;27:455–77.
- Sundin A, Vullierme MP, Kaltsas G, et al. Mallorca Consensus Conference participants, European Neuroendocrine Tumor Society-E-NETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: radiological examinations. *Neuroendocrinology* 2009;90:167–83.
- Chiti A, Fanti S, Savelli G, et al. Comparison of somatostatin receptor imaging, computed tomography and ultrasound in the clinical management of neuroendocrine gastro-entero-pancreatic tumours. *Eur J Nucl Med* 1998;25:1396–403.
- Nunes H, Brillat PY, Valeyre D, et al. Imaging in sarcoidosis. *Semin Respir Crit Care Med* 2007;28:102–20.
- Alavi A, Gupta N, Alberini JL, et al. Position emission tomography imaging in nonmalignant thoracic disorders. *Semin Nucl Med* 2002;32:293–321.
- Carter KR, Kotlyarov E. Common causes of false positive F18 FGD PET/CT scans in oncology. *Braz Arch Biol Technol* 2008;50:29–35.
- Chang JM, Lee HJ, Goo JM, et al. False positive and false negative FDG-PET scans in various thoracic diseases. *Korean J Radiol* 2006;7:57–69.
- Goo JM1, Im JG, Do KH, et al. Pulmonary tuberculoma evaluated by means of FDG PET: findings in 10 cases. *Radiology* 2000;216:117–21.
- Turkington TG, Coleman RE. Clinical oncologic positron emission tomography: an introduction. *Semin Roentgenol* 2002;37:102–9.
- Bakheet SM, Powe J. Benign causes of 18-FDG uptake on whole body imaging. *Semin Nucl Med* 1998;28:352–8.
- Brudin LH, Valind SO, Rhodes CG, et al. Fluorine-18 deoxyglucose uptake in sarcoidosis measured with positron emission tomography. *Eur J Nucl Med* 1994;21:297–305.
- Bajetta E, Catena L, Ducceschi M, et al. Pitfalls in the diagnosis of neuroendocrine tumors: atypical clinical and radiological findings as cause of medical mistakes. *Tumori* 2009;95:501–7.