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MINI-REVIEW

Pancreatic nodule positive for 68-Ga-DOTAPEPTIDE-PET: NET or ectopic spleen? The importance of a good differential diagnosis

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Abstract

Background Accessory spleen is a congenital defect in which splenic tissue is present outside the spleen. In 20% of cases, accessory spleen is localized within the pancreatic tail, a condition known as IPAS. The identification of this benign anomaly, which affects about 2% of general population, is not easy because it is often mistaken for a pNET which is more common, at around 5%. A 68-Ga-DOTAPEPTIDE-PET normally identifies pNETs with high rate of sensitivity and specificity, but in some conditions, it produces false positives, including IPAS.

Materials and tools A clinical case we recently encountered, prompted us to review the available medical literature on the topic. Typing "intrapancreatic accessory spleen" into PubMed database and limiting research to the last 10 years yielded 121 results from which we selected the most relevant articles for decision-making, with a brief explanation of the reasons for selecting those. Our analysis focused on the most critical and least descriptive articles, those which clearly indicated the importance of differential diagnosis by promoting the use of advanced investigations in case of pancreatic nodule suspected for IPAS. Ultimately, our objective was to update the available guidelines recommendations.

Discussion and conclusions Despite concern in the medical literature, a differential IPAS diagnosis is still subordinate to other clinical, radiological, nuclear medicine, and cytological criteria. After reviewing the literature, we recommend that IPAS should always be considered as a possibility before diagnosis of pNET is made. IPAS should be suspected in the presence of the following findings: asymptomatic pancreatic nodule found incidentally, absence of laboratory findings of NETs, localization in the pancreatic tail, between 1 and 3 cm in size with well-defined margins, homogeneous enhancement, and similar attenuation to the spleen on CT and MRI. In these cases, the use of advanced investigations beyond 68-Ga-DOTAPEPTIDE-PET must be systematic. The recognition of IPAS is not only a diagnostic refinement, but it also avoids unnecessary surgery for the patient.

Keywords Pancreatic neuroendocrine tumors (pnets) · Intra pancreatic accessory spleen (IPAS) · Ectopic/heterotopic spleen · Differential diagnosis

Background

Accessory spleen is a congenital abnormality consisting of normal splenic tissue in ectopic sites. It arises as a failure of fusion between some of the multiple buds of splenic tissue in the dorsal mesogastrium during embryologic life. This ectopic tissue can be found, in order of frequency, in the following: splenic hilum (80%), pancreatic tail (20%), stomach, bowel, and genitals [1, 2]. In autoptic studies, ectopic spleen has an incidence of 10%, and intra-pancreatic accessory spleen (IPAS) an incidence of 2% [3]. Although still uncommon, their clinical incidence is growing probably due to the improvement of diagnostic imaging accuracy.

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Very occasionally, a specific abdominal pain or idiopathic thrombocytopenic purpura (not responsive to splenectomy) is present in patients with IPAS [4]. Because it is asymptomatic, IPAS is almost always found incidentally as an undefined pancreatic mass similar to NETs. The frequency of functional pancreatic NETs (f-p-NETs), similar to that of non-functional pancreatic NETs (nf-p-NETs), is increasing, again probably due to the widespread use of high-quality imaging techniques [5–7]. Recent studies have shown imaging with 68-Ga-labeled somatostatin analogs with PET/CT, to be highly sensitive and specific for pNETs; nevertheless cases of IPAS can give false positives.

Materials and tools

Case report

A 56-year-old man came to the attention of neurologists with a clinical picture characterized by limb hyposthenia, weight loss, and fatigue. Dilation of aortic bulb, hypertension, and prostatic hypertrophy are the only concomitant conditions in the patient's medical history. After the onset of symptoms, the patient underwent several diagnostic tests which failed to establish a cause. Neurologists first excluded the main microbiological, viral, and parasitological causes which may have led to nervous system involvement with post-infectious syndromes such as Guillain–Barré disease. They then suspected an autoimmune disease such as multiple sclerosis; therefore, the patient underwent a CT of the brain and a lumbar puncture, but both were also negative. The patient was subjected to specialist investigations such as electromyoneurography and somatosensory evoked potentials but these examinations were also inconclusive. Subsequently the patient was studied by endocrinologists and their investigations were absolutely normal.

Finally, the patient was referred to oncologists with the clinical suspicion of a paraneoplastic syndrome. Total-body CT scan showed a 15 mm oval lesion in the pancreatic tail, visible only in arterial phase, with possible expression of pNET (Fig. 1). The patient did not report specific symptoms of neuroendocrine syndrome, and tumor markers of this condition were within the normal levels (Chromogranin A was 45 ng/ml with normal laboratory range 0–108 and enolase, neuron specific, was 2 ng/ml with normal laboratory cut-off < 15.2). The patient was unable to perform an MRI due to the presence of a metal plate in the left leg (surgical correction of previous traumatic fracture).

The next step for the diagnosis of a possible nf-p-NET was to perform a 68-Ga-DOTAPEPTIDE-PET/CT which demonstrated an increased uptake of metabolic tracer (SUV_{max} 18) within the known lesion in the pancreatic tail (Fig. 2).

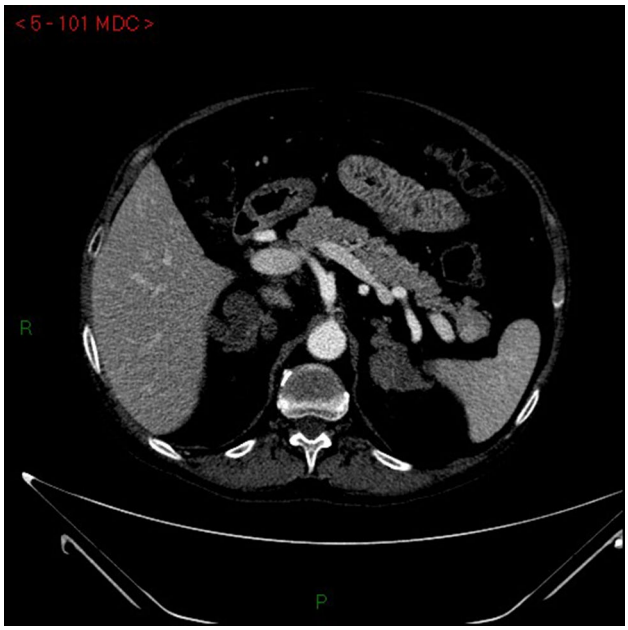

Fig. 1 Axial CT scan showing nodular lesion in the pancreatic tail

The rationale for using this nuclear medicine examination derives from the fact that the majority of NETs expresses somatostatin receptors (SSTR) which can be used as targets for radionuclide imaging. 68-Ga-DOTAPEPTIDES binds SSTR, mainly SSTR2, the receptor subtype predominantly expressed in NETs [8].

From a technical point of view, PET/CT acquisition starts at 60 min after intravenous injection of approximately 100 MBq (75–250 MBq) of the radiolabeled peptide. The amount of injected radioactivity strictly depends on the daily production of the generator for each single elution (usually ranging between 300 and 700 MBq) and, of course, by the number of patients scanned per day. No specific patient preparation is required. The use of contrast media is not routinely recommended [9].

Together with the information gained before, the accumulation of radiotracer in the pancreatic nodule suggested a likely diagnosis of nf-p-NET.

The patient underwent distal splenopancreasectomy with excellent recovery after surgery and was discharged. Pathological findings revealed a soft and red-brown pancreatic nodule, 1.3 cm in diameter, consistent with it being heterotopic spleen tissue within the pancreatic parenchyma (Fig. 3).

Nuclear medicine examinations for IPAS diagnosis

The above clinical case suggests 68-Ga-DOTAPEPTIDE-PET could be a diagnostic pitfall; therefore, to make an

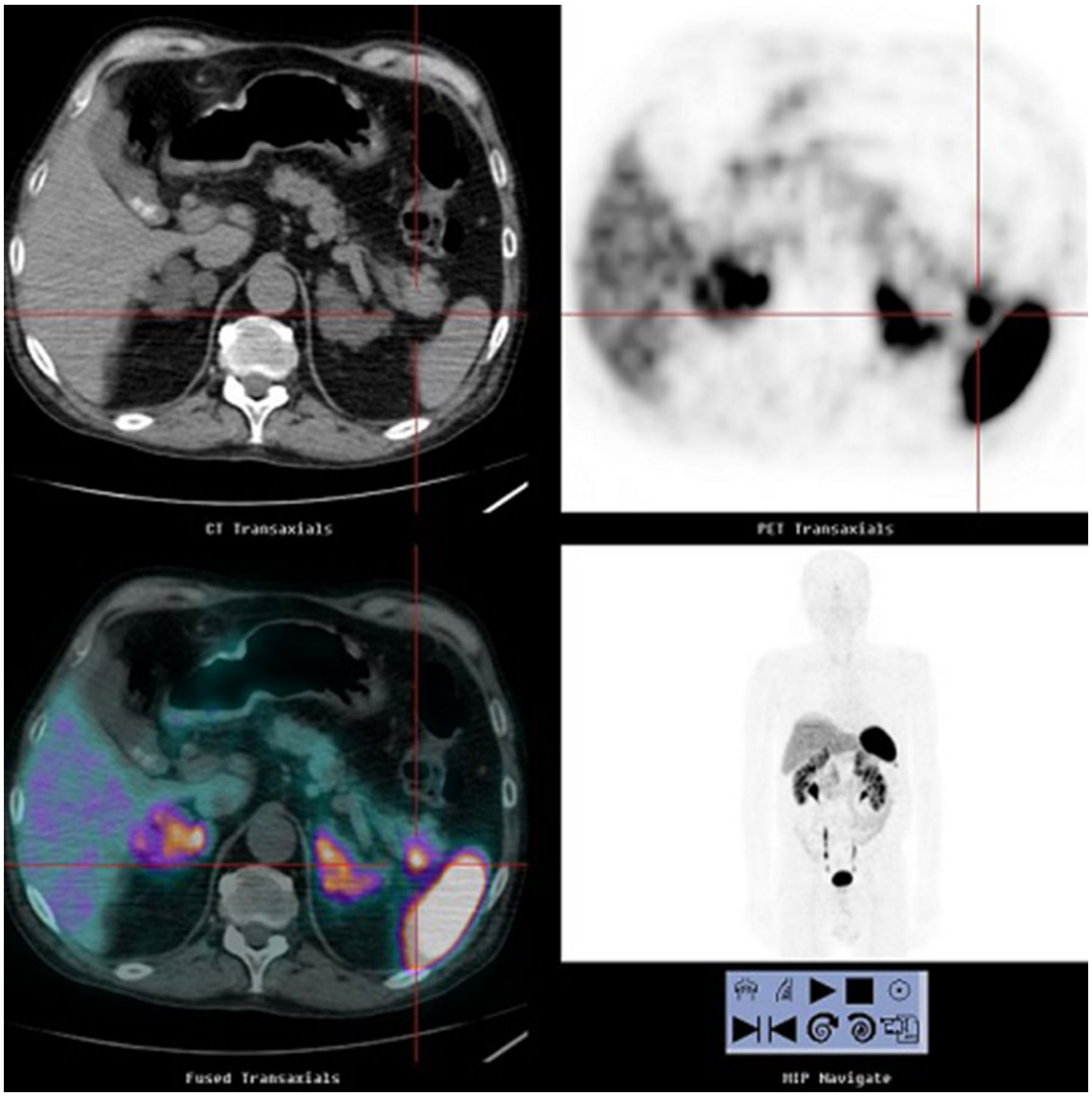

Fig. 2 Increased uptake of radiotracer by the same pancreatic lesion of 68-Ga-DOTAPEPTIDE-PET

accurate diagnosis of a focal pancreatic lesion, it is better to use advanced level examinations.

The role of nuclear medicine could become crucial in IPAS diagnosis if it were to be routinely used in the patient's imaging management. Two main tests have been demonstrated to have a high diagnostic accuracy: Technetium-99 m heat-damaged red blood cell SPECT and Technetium-99 m nanocolloids scintigraphy. Their rationale for use derives from the fact that both denatured red blood cells and nanocolloids are incorporated by the reticulo-endothelial system thus allowing visualization of the spleen and any accessory spleens.

Technetium-99 m heat-damaged red blood cell SPECT is very laborious because it involves a particular treatment protocol of patient's red blood cells. First, a solution of sodium pyrophosphate is injected intravenously, then a venous sample is withdrawn into a heparinized syringe containing 740 MBq of Technetium-99 m, and after intermediate stages, the blood is reinjected into the patient and finally the acquisition of the images is made [10].

Technetium-99 m nanocolloids scintigraphy was developed to obviate the problem of complexity of the previous examination. To perform this test, the administration of nanocolloids does not require any particular protocol and the duration of examination is approximately 45 min. Splenic scintigraphy has, therefore, established itself as an economical, accessible, and accurate tool for IPAS diagnosis [11].

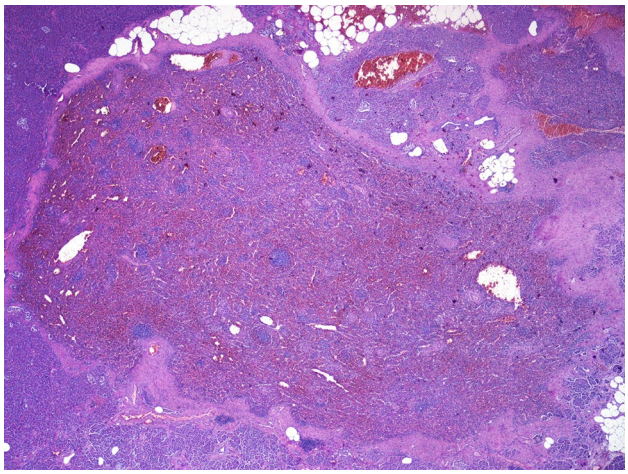

Fig. 3 Histological picture of IPAS. The image clearly shows the area of splenic tissue composed internally by the red and white pulp and well defined by a fibrous outline which separates it from the surrounding pancreatic parenchyma

Literature analysis

An analysis of recent publications on the diagnosis and management of IPAS was performed: typing "intrapancreatic accessory spleen" into PubMed web search engine, the official database of USA-NIH (National Institutes of Health) and limiting research to the last 10 years, we obtained 121 results which mainly consist of case reports and short reviews. In this section, we highlight the most useful articles for decision-making, introducing each of them with a brief explanation of the reasons for selecting them.

Our analysis focused on the most critical and least descriptive articles, those which clearly indicated the importance of differential diagnosis by promoting the use of advanced investigations in case of pancreatic nodule suspected for IPAS.

The Table 1 at the end of this section summarizes the main features of selected papers.

The first article selected is that of Kurmann and colleagues which deals with the topic of misdiagnosis describing the biological reasons why nuclear medicine examinations, based on somatostatin analogs, can produce false positive. Lymphocytes of splenic tissue express somatostatin receptors which bind to molecular analogs with high affinity, mimicing a NET; consequently these authors recommended the need for preoperative evaluation of patients with pancreatic lesions, using more sophisticated investigations such as nanocolloids scintigraphy or Technetium-99 m heat-damaged red blood cells SPECT, to provide the definitive diagnosis of IPAS [12].

A crucial point of all radiological and diagnostic imaging has been the attempt to define essential criteria to assist an IPAS diagnosis suggested by conventional examinations like CEUS, CT or MRI. The following two publications develop this aspect.

Makino et al. proposed using CEUS with Sonazoid, a recent contrast solution, for the identification of ectopic spleens, because it is a non-invasive examination which is able to recognize the particular pattern of the reticulo-endothelial cell system typical of splenic tissue [13].

Spencer et al. published an article which defined the main radiological criteria for achieving a differential diagnosis among IPAS, pNET and pancreatic metastases following CT and MRI. CT and MRI can provide preliminary information to raise suspicions of IPAS, but nuclear medicine tests have greater diagnostic accuracy. Similar density/intensity of spleen on all phase/sequences and homogenous enhancement, represent the main imaging features to suspect the presence of IPAS [14].

Where a malignant lesion is suspected, and before planning surgery, it is always appropriate to obtain, when feasible, a biopsy sample of lesion and applying this medical rule, Lin and colleagues, demonstrated that cytological evaluation by EUS-FNA, linked to the patient's clinical and radiological data, is the most efficacious tool for making the diagnosis of IPAS [15].

But EUS-FNA, like all diagnostic investigations, has its limitations. Bergeron and colleagues, collected an interesting series of 1212 EUS-FNA procedures describing the benefits but also the potential pitfalls of this technique; their

Table 1 Summary of the main features of selected articles

First author	References note number	Journal and year of publication	Reasons for selecting article
Kurmann et al	[12]	Case reports in gastroenterology; 2010	Biological rational of 68-Ga-DOTAPEPTIDE-PET pitfall
Makino et al	[13]	Journal of clinical ultrasound;2011	Diagnostic utility of Sonazoid-CEUS
Spencer et al.	[14]	The British journal of radiology; 2010	Role of CT and MRI in differential diagnosis
Lin et al.	[15]	Archives of pathology and laboratory medicine; 2010	The crucial importance of cytological diagnosis of IPAS by EUS-FNA
Bergeron et al	[16]	Cancer cytopatholgy; 2015	The difficulties and limitations of cytological diagnosis
Baugh et al.	[17]	Journal of surgical research; 2019	A management algorithm for IPAS diagnosis

work, conducted in an extremely rigorous way, reported the relative percentages of benign, malignant and non-diagnostic pancreatic lesions. The main difficulty in EUS-FNA cytological examination is to distinguish mucinous pancreatic cancer from the contaminants of gastric mucosa. In addition, another and insidious pitfall is represented by IPAS and, in this regard, the authors suggested performing an accurate cytological evaluation [16].

The last article we propose has a summary nature because it presents a diagnostic algorithm for pancreatic incidentalomas, emphasizing the importance of integration among medical investigations. Following on from this, Baugh and colleagues, propose starting with radiological and nuclear medicine investigations, to get a first picture of diagnostic hypotheses. In cases with suggestive radiological features for IPAS, the algorithm countermands use of 68-Ga-PET EUS-FNA and reserves surgery for only cyto/histologically proven pNETs and potentially malignant lesions [17].

Guideline recommandations

In this paragraph, we summarize European and American guidelines on the topic. The European Neuroendocrine Tumors Society (ENETS) Consensus Guidelines suggest choosing MRI as a preliminary examination to distinguish pNETs from IPAS and for doubtful cases, it clearly refers to advanced level investigations [18].

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) has always been committed to promoting nuclear medicine examinations not so much as sophisticated tests to be reserved for a few patients, but just as complementary investigations for radiological ones in imaging studies of human diseases. For the purpose of our objective the Society published, in collaboration with the American College of Radiology (ACR) and the Society for Pediatric Radiology (SPR), a practice guideline for procedure standards for liver and spleen scintigraphy to identify splenic tissue in the natural and ectopic sites [19].

Discussion and conclusions

IPAS is a benign congenital abnormality, usually asymptomatic and incidentally diagnosed through imaging examination made for other reasons [20, 21]. Being inside the pancreas, IPAS simulates a solid tumor of the gland which prompts clinicians to immediately start the diagnostic–therapeutic process, considering the bad prognosis of pancreatic cancer. The lack of symptoms typical of cholestatic jaundice or neuroendocrine syndrome, suggests the presence of a silent tumor such as nf-p-NETs. After conventional examination and exclusion of pancreatic adenocarcinoma or other lesions, patients undergo a 68-Ga-DOTAPEPTIDE-PET and positivity in this investigation normally concludes the diagnostic process [22]. The patient is then referred to surgery to eventually find out that histological evaluation of the biopsy reveals an IPAS. This pathway typifies daily clinical practice and not by chance our clinical report and all those presented in medical literature expose this same descriptive sequence.

Despite the concerns raised by these articles, IPAS diagnosis is still ignored today and the main reasons for this are epidemiological, clinical, and diagnostic: epidemiologically the condition is rare; clinically, IPAS presents with few symptoms and the current medical approach is to consider pancreatic lesions as malignant; and finally the diagnostic reason is the 68-Ga-DOTAPEPTIDE-PET pitfall.

The original aim of our article was to have made a critical and updated review of the medical literature, and to underline the importance of a good differential diagnosis between pNET and IPAS that is based on a series of essential criteria which should never be disregarded.

In conclusion, we recommend that IPAS should be suspected in the presence of the following findings: asymptomatic pancreatic nodule found incidentally; absence of laboratory findings of NETs; localization in the pancreatic tail; between 1 and 3 cm in size with well-defined margins; homogeneous enhancement and similar attenuation to the spleen on CT and MRI. A combination of radiological and nuclear medicine imaging investigations as well as EUS-FNA might be required for IPAS diagnosis because none of them are individually conclusive. IPAS recognition does not represent only a diagnostic refinement but it also has a practical benefit for patients because, being a benign condition, it does not require surgery.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest.

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