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PANCREATIC SPLENOSIS MIMICKING NEUROENDOCRINE TUMORS: microhistological diagnosis by endoscopic ultrasound guided fine needle aspiration

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ABSTRACT - ***Context*** - Pancreatic splenosis is a benign condition which can mimic a pancreatic neoplasm. ***Objective*** - To describe the role of the endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) of pancreatic nodules suspicious for pancreatic splenosis. ***Method*** - From 1997 to 2011, patients with pancreatic solid tumors suspicious for splenosis by computed tomography and/or magnetic resonance imaging were referred to EUS-FNA. Those cases with pancreatic splenosis confirmed by EUS-FNA or surgery were included. Endosonographic findings and clinicopathologic features were also analysed. ***Results*** - A total of 2,060 patients with pancreatic solid tumors underwent EUS-FNA. Fourteen (0.6%) cases with pancreatic splenosis were found. After applying exclusion criteria, 11 patients were selected. Most patients were male (7), young (mean age: 42 years) and asymptomatic (8). Endoscopic ultrasound imaging alone suspected pancreatic splenosis in 6 cases, and neuroendocrine tumors in 5 cases. Pancreatic splenosis was found most commonly in the tail, was round, hypoechoic, with homogeneous pattern, regular borders, and with scintigraphy negative for somatostatin receptors. The average diameter of these nodules identified by endoscopic ultrasound was 2.15 cm. Microhistology obtained by EUS-FNA confirmed the diagnosis in 9/10 patients. ***Conclusion*** - Pancreatic splenosis can be diagnosed by EUS-FNA. Microhistology prevents unnecessary surgeries, and reassures asymptomatic patients with hypoechoic, homogeneous, and well circumscribed pancreatic nodules.

HEADINGS - Pancreatic neoplasms. Neuroendocrine tumors. Splenosis. Endosonography. Biopsy, fine-needle.

INTRODUCTION

Abdominal splenosis is the spontaneous transplantation of splenic tissue to unusual sites[8]. This situation usually occurs after splenic trauma or surgery. Another cause is the failure of coalescence during migration of mesenchymal cells of the splenic primordium[15]. The deposition of isolated cells from the spleen appears as bluish-red nodules, which can affect the peritoneum, mesentery, liver, kidney and pancreas[8, 15]. Pancreatic splenosis (PS) is found, in most cases, by chance and does not require surgical resection once accurately diagnosed[14]. However, PS can be confounded with a pancreatic nonfunctioning neuroendocrine tumor (NET) due to its imaging findings and hypervascular nature[16]. For this reason, precise diagnosis is crucial, as PS does not require surgical treatment[15]. Scintigraphy for somatostatin receptors is the method of choice for diagnosis of NETs, but it still can fail to confirm the tumor in a significative number of cases[15].

The aim of this study was to describe the clinical and endosonographic findings, as well as demonstrate the value of microhistology obtained by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) for the diagnosis of pancreatic splenosis.

METHOD

From January 1997 to October 2011, 2,060 patients with solid pancreatic tumors underwent EUS-FNA at Endoscopic Ultrasound Units from Hospital 9 de Julho, São Paulo, SP, and Hospital das Clínicas, Ribeirão Preto Medical School, Ribeirão Preto, SP, Brazil. In this retrospective study, patients were selected based on pancreatic nodules suspicious for splenosis

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by computed tomography (CT) and/or magnetic resonance imaging (MRI), who were evaluated by EUS, and submitted to FNA with microhistology analysis. Patients with splenosis or accessory spleen located around the pancreatic tail were excluded. The following data were recorded: demographics, imaging findings, and clinicopathologic features.

Once obtained the informed consent for the procedure, patients were sedated with propofol associated with midazolam and fentanyl under cardiorespiratory monitoring. All procedures were performed by the same echoendoscopist with extensive experience in diagnostic and therapeutic echoendoscopy (JCA). The sectorial echoendoscopes used were: Pentax FG 38-UX (Pentax Precision Instruments Corp., Orangeburg, NY, USA) coupled to an ultrasound unit Hitachi EUB 515 (Mitsubishi, Conshockon, Phila, USA), Olympus UCT-160 OL5 (Olympus Optical Corp., Ltd., Tokyo, Japan) coupled to an ultrasound unit UC-60 (Suzy-Olympus Optical Corp. Ltd., Tokyo, Japan), and Fujinon EG-530UT (Fujifilm Optics Corp. Ltd., Sano, Japan) coupled to an ultrasound unit SU7000 (Kodai Hi Tec Corp. Ltd., Saitama, Japan). Only needles of 22 gauge and length of 145 cm (Medi Globe, Medizintechnik GMBH, Grassau/Germany) were used for the punctures. Color Doppler was used to ensure the absence of vascular structures along the path of the needle and to assess whether the lesion was hypervascular. The endosonographic features took into account were: location, size, shape, borders, echotexture, and homogeneity. After puncturing the tumor, core specimens were obtained by flushing the needle with 2 mL of saline and then by reintroduction of the stylet inside the needle. All material was placed in 10% buffered neutral formalin solution. As an on-site cytopathologist was not available in our routine, the specimens were considered satisfactory in the presence of non-hemorrhagic small tissue filaments or tissue core samples. The specimens were sent to pathologist with expertise in pancreatic pathology (FV), and prepared according to a previously described cell block technique[2]. Diagnosis of PS was based on demonstration of aggregates of splenic tissue, with red and white pulp, scarce pancreatic acinar tissue, and, in the presence of specimens enough for analysis, immunohistochemical studies for synaptofisin and chromogranin-A.

Statistical analysis

Demographics, clinical features, endosonographic and pathologic findings were recorded. Continuous variables were described as mean and standard deviation, and dichotomous variables were expressed as simple ratios.

This study was approved by the Ethics Committee of both institutions. Beforehand, every patient gave his/her informed consent for the EUS-FNA of pancreatic nodules, and for evaluation of the specimens by microhistology techniques. The protocol of this study followed the parameters and ethical rules established by the Declaration of Helsinki of World Medical Association, which regulates ethical principles involving medical research on humans.

RESULTS

Overall, 14 (0.6%) patients were selected. After applying exclusion criteria, we selected 11 cases with a mean age of 42.3 years (range: 20-56 years). Demographics, imaging and pathology findings of these cases are presented in the Table 1. Most of these patients were men [seven (63%)] and

TABLE 1. Demographics, imaging and pathology findings of pancreatic splenosis

n	Age	Gender	History	Symptoms	trauma	CT	MRI	Cyntigraphy	EUS diagnosis	Size (cm)	Shape	Site	Echotexture	Border	Micro-hystology	IHC
1	20	F	Asymptomatic	No	No	Nodule	NA	NA	NET	1.5x1.2	round	Tail	Homogenous	Well-defined	PS	No
2	70	F	Ovarian tumor (Rt/Qt)	No	Yes	Nodule	Nodule	NA	NET	1.5x1.2	round	Tail	Homogenous	Well-defined	NET	No
3	42	M	Epigastric Pain	Yes	No	NA	Nodule	Neg	PS	1.3x1.0	Oval	Tail	Homogenous	Well-defined	PS	Yes
4	43	M	Cirrhosis	No	No	Nodule	Nodule	Neg	NET	3.5x1.9	Oval	Tail	Homogenous	Well-defined	PS	Yes
5	50	M	Asymptomatic	No	Yes	Nodule	NA	Neg	PS	2.1x0.9	Oval	Head	Homogenous	Well-defined	PS	Yes
6	20	M	Acute pancreatitis	Yes	Yes	Nodule	Nodule	Neg	NET	3.6x1.5	Oval	Tail	Heterogenous	Ill-defined	PS	Yes
7	30	F	Asymptomatic	No	No	NA	Nodule	PS (?)	PS	1.8x1.4	round	Tail	Homogenous	Well-defined	PS	Yes
8	30	M	Acute pancreatitis	Yes	Yes	Nodule	Nodule	Neg	PS	3.4x2.7	round	Tail	Homogenous	Well-defined	NA	Yes
9	56	M	Asymptomatic	No	No	Nodule	Nodule	NA	NET	1.2x1.0	round	Body	Homogenous	Well-defined	--	No
10	48	F	Asymptomatic	No	No	Nodule	Nodule	PS (?)	PS	1.9x1.7	round	Tail	Homogenous	Well-defined	PS	No
11	56	M	Asymptomatic	No	Yes	Nodule	NA	NA	PS	1.8x1.4	round	Tail	Homogenous	Well-defined	PS	Yes

NA: not available

NET: neuroendocrine tumor

IHC: imunohystochemistry

asymptomatic [eight (73%)]. Three (27%) cases presented abdominal pain. Previous history of abdominal trauma was detected in four (36%) cases [blunt abdominal trauma (two) and car accident (two)], and one (10%) patient had previous abdominal surgery for ovarian cancer. Six (54%) patients had no report of abdominal trauma or surgery.

Imaging findings of round pancreatic nodule in the tail obtained by CT and/or MRI, with well-defined borders, showing the same echotexture of the spleen, and positive scintigraphy for somatostatin receptors, were not enough to think about splenosis in two (18%) cases (Figure 1).

Primary indications for EUS-FNA were: suspicious for nonfunctioning NET (eight), PS (two) and lymphoma (one). EUS imaging alone suspected PS in six (54.5%) cases, and nonfunctioning NET in five (45.5%) cases. The number of nodules identified by EUS was 13 in 11 patients. Nodules were found in the tail (nine), head (two), body (one) and around the pancreatic head (one). The lesions were solitary in most cases (10), and 1 patient had three lesions, 2 in the pancreatic head, and another one around the pancreatic head. EUS revealed round (seven) and oval nodules (four), with average diameter of 2.15 cm.

EUS-FNA was successful in 10/10 patients with an average of 2.2 passes (range: 2-3) without any complication. Final diagnosis was obtained by microhistology (Figure 2) in 9/10 (90%) cases. Immunohistochemistry was performed in 7/10 cases (70%), and all these cases were negative for synaptofisin and chromogranin-A. In a single case, EUS-FNA made the diagnosis of a neuroendocrine tumor, which was modified to splenosis after subtotal pancreatectomy without splenectomy. Another false-positive for NET, also referred to surgery, occurred in a patient not submitted to FNA who was evaluated by EUS imaging alone (Figure 3).

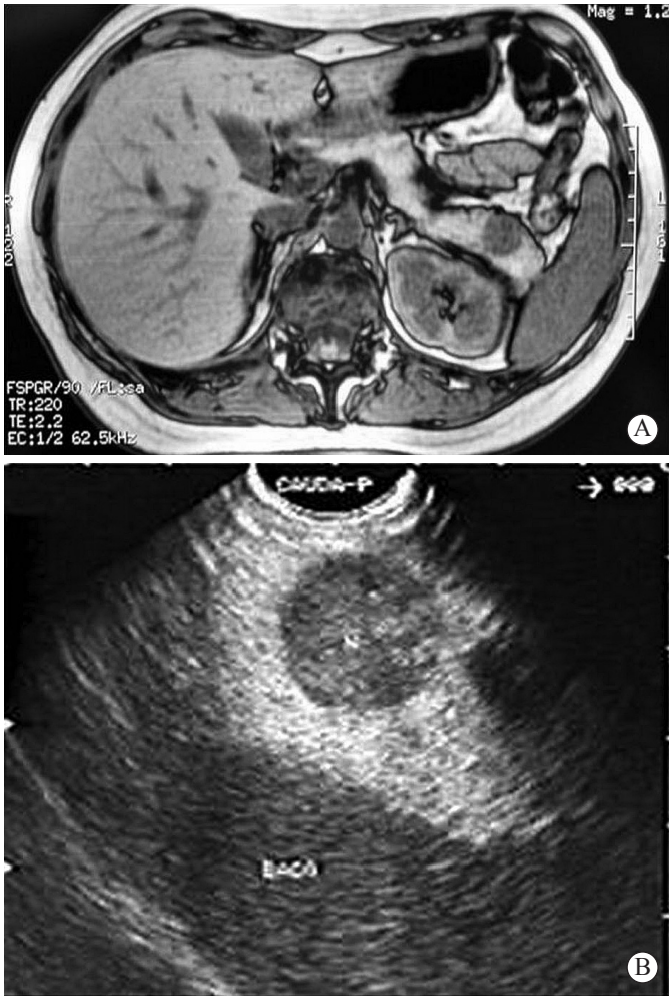

FIGURE 1. Asymptomatic patient (no. 10) with (a) MRI showing a round, hypointense pancreatic nodule in the pancreatic tail, measuring 1.9 x 1.7 cm. (b) EUS shows a hypoechoic, homogeneous, and regular nodule with well-defined borders. Echogenicity is similar to the spleen. FNA made diagnosis of PS

DISCUSSION

Pancreatic splenosis occurs usually after splenic trauma, such as automobile accidents, stab or gunshot wounds, and surgery. This occurred in almost 46% of our patients. On

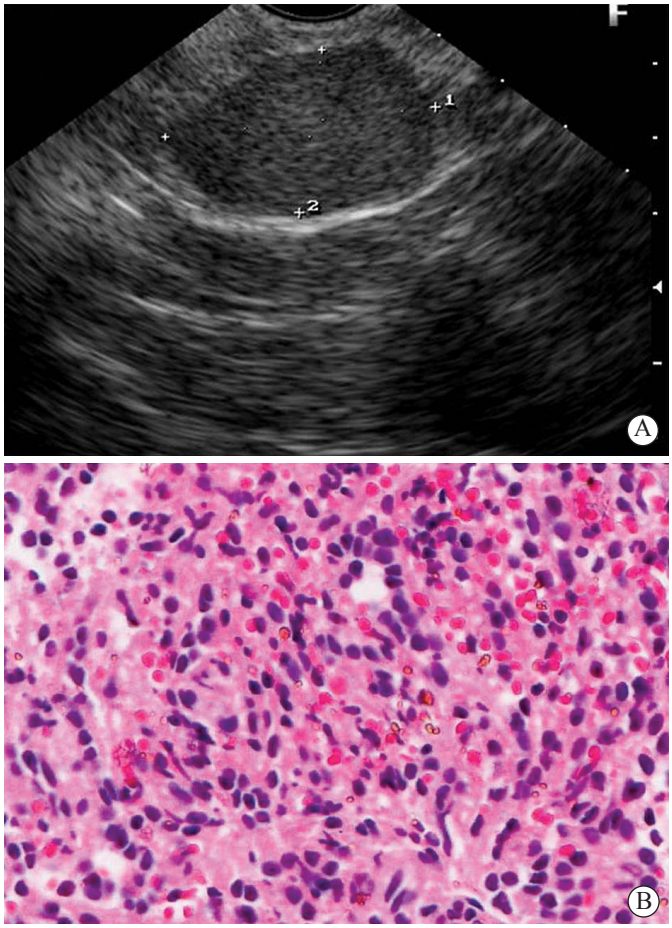

FIGURE 2. Patient no. 9 with (a) EUS findings, and (b) microhistology showing pancreatic splenosis. (Hematoxylin-eosin; magnification:200x)

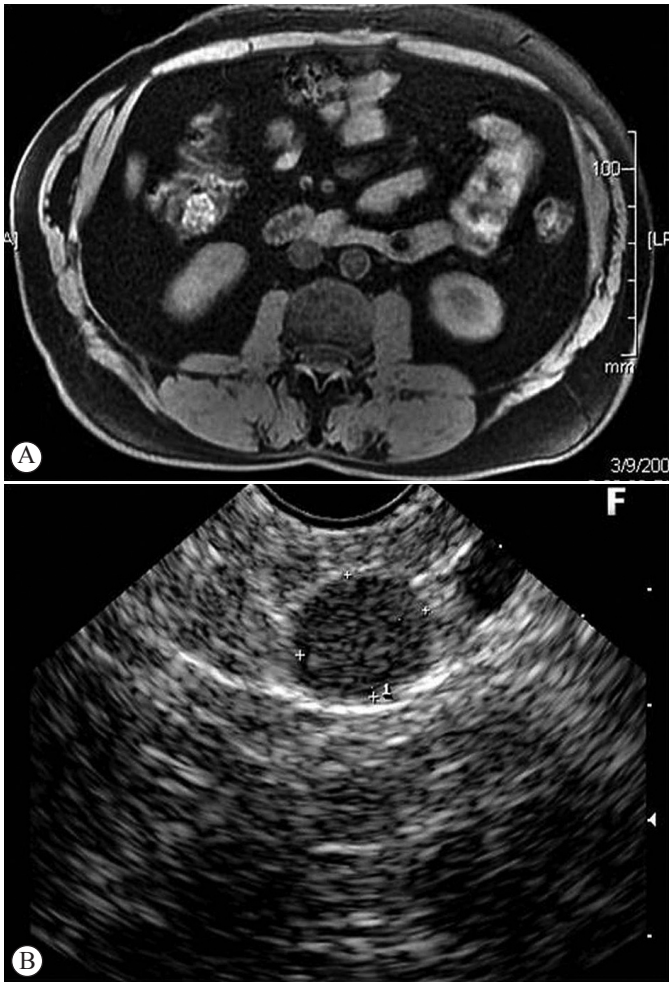

FIGURE 3. Asymptomatic patient (no. 2) with (a) MRI showing an isolated and hypointense nodule in the pancreatic body. EUS reveals a round, hypoechoic, homogeneous, and regular nodule with well-defined borders, measuring 1.2 x 1.0 cm. EUS was suspicious for NET and FNA was not performed. Surgical diagnosis was PS

the other hand, when there is no history of trauma, another explanation is a developmental disorder around the 5th week of gestation, in which isolated splenic cells are shed from the spleen to the pancreas[5].

Autopsy studies revealed abdominal splenosis in 10%-30% of the patients[5, 10]. In other study in which 1,000 patients underwent CT, abdominal accessory spleen was found in 16% of the patients[20]. In 80% of these cases, accessory spleen was located near the splenic hilum. The second most common site was the tail of the pancreas (17%)[10]. In our series, PS was found in 0.6% of the patients with pancreatic nodules submitted to EUS-FNA. Although a benign lesion**,** PS can mimic a pancreatic neoplasm, and the differential diagnosis comprises pancreatic carcinoma, NET, solid-cystic papillary tumor and metastases[2].

Pancreatic NETs are rare, accounting for less than 10% of the pancreatic solid tumors, and are often located in the pancreatic head[1, 6, 21]. These tumors are symptomatic in 15% to 53% of the cases due to secretion of biologically active substances. The remaining are nonfunctioning and usually asymptomatic, although 50% are malignant and require surgical resection[6, 13].

The literature reports 13 cases of accessory spleen simulating pancreatic tumors, all of them submitted to surgical resection[7, 15, 25]. In our series, two patients were submitted to surgery for suspicion of NETs, both of them due to false-positive diagnoses, one case by the microhistology evaluation, and the other one by the EUS imaging alone in a patient not submitted to FNA. In regard to imaging assessment, PS is a round and homogeneous lesion with well-defined borders[3]. Most of these lesions are small, less than 2 cm in diameter[9]. However, a definitive diagnosis of PS based on imaging alone can be difficult because CT, MRI and EUS images are very similar to those found in hypervascular pancreatic tumors such as islet cell tumors and acinar cell carcinoma[7, 18, 22, 23]. In our experience, EUS imaging misinterpreted pancreatic nodules, round, homogeneous and with well-defined borders as a NET in 45.5% of the cases. All of these patients have previously been submitted to other imaging procedures (CT and/or MRI) and the echoendoscopist was not blind for these results. Despite their poor contribution for the diagnosis of splenosis, this fact could have influenced the diagnosis of EUS imaging alone. These results are similar to those found by Barawi et al.[3]. These authors highlight that PS or a splenic lobulation can also be misinterpreted as malignant tumors by EUS imaging alone. Besides, PS can be hyperechoic (a fact that did not occur in any of our cases) with a homogeneous pattern, which could complicate much more the differential diagnosis of pancreatic nodules based only on EUS imaging. These authors point out that a regular margin and the anatomic location could help prevent misdiagnosis. In addition, CT could be useful to confirm the diagnosis[3]. Unlike the experience by Barawi et al.[3], CT and MRI did not identify PS in our series.

Somatostatin receptor scintigraphy has high sensitivity for detection of gastrointestinal NETs (70%-95%), but false-positive results can occur, specially for small lesions[17]. This is due to the presence of somatostatin receptors on the surface of lymphocytes in the ectopic splenic tissue, which also have high affinity to octreotide, mimetizing a neuroendocrine tumor[17, 19]. In the experience by Heredia et al.[11], gadolinium MRI suspected splenosis in 3/5 patients, but it was not capable to exclude other diagnoses, including NETs, solid-cystic pseudopapillary adenocarcinoma and metastasis. In our series, MRI raised a suspicion for a PS in only one case.

Medical literature refers only three articles about the role of EUS-FNA in the diagnosis of PS[4, 12, 24]. These three studies reported 10 cases of PS in pancreatic tail with a sensitivity of 100%. Any diagnostic method should be used in an attempt to increase the accuracy in favor of PS and, this way, avoid unnecessary surgeries. In our series, microhistology obtained by FNA confirmed the diagnosis of PS in 90% of the cases. We had only a false-positive result for a NET in the beginning of our experience.

CONCLUSIONS

Echoendoscopic findings of pancreatic splenosis can be challenging. Even for the most common finding - an hypoechoic, homogeneous, and well circumscribed nodule - EUS-FNA should be mandatory to confirm the lesion as a neuroendocroine tumor or a pancreatic splenosis. The identification of spleen tissue by microhistology obtained by EUS-FNA prevents not only an unnecessary surgery for small nodules, but also reassures a young asymptomatic patient with a pancreatic nodule.

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RESUMO - ***Contexto*** - A esplenose pancreática é uma afecção benigna que pode mimetizar uma neoplasia pancreática. ***Objetivo*** - Descrever o papel da ecoendoscopia associada à punção aspirativa com agulha fina ecoguiada (EE-PAAF) dos nódulos de pâncreas suspeitos de esplenose pancreática. ***Método*** - De 1997 a 2011, pacientes com tumores sólidos de pâncreas sugestivos de esplenose pancreática, conforme achados de exames de imagem por tomografia computadorizada e/ou ressonância magnética foram encaminhados para EE-PAAF. Os casos com esplenose pancreática confirmada pela ecoendoscopia ou pela cirurgia foram incluídos. Os achados endossonográficos e os aspectos clinicopatológicos foram analisados. ***Resultados*** - Dois mil e sessenta pacientes com tumores sólidos do pâncreas foram submetidos a EE-PAAF. Quatorze (0,6%) casos com esplenose pancreática foram encontrados. Após emprego dos critérios de exclusão, 11 pacientes foram selecionados. A maioria dos pacientes era do sexo masculino (7), jovens (idade média: 42 anos) e assintomáticos (8). A imagem ecoendoscópica isolada suspeitou de esplenose pancreática em 6 casos, e tumores neuroendócrinos em outros 5 casos. A esplenose pancreática foi detectada mais comumente na cauda do pâncreas, era redonda, hipoecogênica, com padrão homogêneo, bordos regulares bem delimitados e com cintilografia negativa para os receptores de somatostatina. O diâmetro médio dos nódulos foi de 2,15 cm. A microhistologia obtida pela EE-PAAF confirmou o diagnóstico em 9/10 pacientes. ***Conclusão*** - A esplenose pancreática pode ser diagnosticada pela punção aspirativa com agulha fina ecoguiada. A microhistologia evita cirurgias desnecessárias e tranquiliza pacientes assintomáticos com nódulos pancreáticos hipoecogênicos, homogêneos e com bordos bem definidos.

DESCRITORES – Neoplasias pancreáticas. Tumores neuroendócrinos. Esplenose. Endossonografia. Biopsia por agulha fina.

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