Acute obstructive jaundice: a possible clinical manifestation of IPMT

Case report and review of the literature

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Acute obstructive jaundice: a possible clinical manifestation of IPMT. Case report and review of the literature.

INTRODUCTION: *Pancreatic masses causing acute obstructive jaundice still pose diagnostic difficulties and their characterization can often be complex as there is significant overlap in their imaging features.*
CASE REPORT: *We describe a case of Intraductal Papillary Mucinous Tumor (IPMT) presenting with acute obstructive jaundice in a patient with history of recurrent mild pancreatitis. Clinical evaluation, abdominal ultrasonography (US) and CT-scan posed suspicion of adenocarcinoma with cystic degeneration of the pancreatic head or mucinous cystadenocarcinoma; magnetic resonance (MR) with magnetic resonance cholangiopancreatography (MRCP) demonstrated the communication of the mass with the main pancreatic duct, posing differential diagnosis between main-duct-IPMT and mucinous cystadenocarcinoma. Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated the presence of a mucus-secreting lesion inside duodenum and duodenal biopsies showed no evidence of neoplastic cells.*
RESULTS: *The patient underwent spleen* preserving total pancreatectomy *that led to histological diagnosis of intraductal papillary mucinous with carcinoma in situ.*
DISCUSSION: The international guidelines for management of IPMT, reported in 2006 and revised in 2012, establish that *the resectability and the absence of an invasive carcinoma are the most important prognostic factors in IPMT. Therefore an early diagnosis and a radical resection are crucial to improve the patient survival and reduce the recurrence rate.*
CONCLUSION: *When an IPMT is suspected, the imaging modalities are essential to pose the diagnosis, maximise the chance to select the right surgical candidate and to perform the best treatment for each patient.*

KEY WORDS: IPMT, Acute obstructive jaundice, Pancreatic surgery

Introduction

Pancreatic neoplasms causing obstructive jaundice include solid and cystic lesions. Cystic lesions of the pancreas comprise both benign entities such as inflammatory pseudocysts or serous cystadenomas and neoplasms with malignant potential such as mucinous cysts or Intraductal Papillary Mucinous Tumors (IPMTs). In these cases, a surgical resection is often required and an adequate identification and diagnosis is crucial to perform the best therapeutic strategy [1,2].

Pancreatic cystic lesions still pose diagnostic difficulties and their characterization can often be complex as there is significant overlap in their imaging features. Different imaging techniques could be useful to identify and differentiate the lesions and establish the surgical resectability. Trans-abdominal ultrasound (US) is often the first imaging examination and in experienced hands could be very useful for diagnosis and preoperative evaluation. Endoscopic retrograde cholangio-pancreatography (ERCP) allows to visualize a mucinous discharge from a widely

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ampulla which is a pathognomonic sign of IPMTs and also to obtain samples for cytological and histological examination. CT-scan and magnetic resonance (MR) with magnetic resonance cholangio-pancreatography (MRCP) permit the differential diagnosis among pancreatic tumors, an accurate evaluation of the relationship with surrounding organs and to detect the presence of mural nodules suspicious for malignant degeneration [1-4].
We describe a case of a non invasive IPMT presenting with acute obstructive jaundice in a patient with history of recurrent mild pancreatitis, with special interest in the evaluation of its resectability with different imaging techniques.

Case Report

A 68 years old Caucasian woman was admitted to our Unit with progressive epigastric and lower back pain for over 3 months associated with nausea, worsening dysphagia, hyperchromic urine and hypochromic stools. The patient reported a history of recurrent upper abdominal pain and weight loss during the last year with 2 previous admissions to the emergency department for worsening of the symptomatology. In both cases the laboratory data and radiological findings did not highlight abnormalities and the clinical symptoms resolved spontaneously some hours after her admission.
The patient was no smoker and had a moderate alcohol consumption. Past medical and surgical history included hypercholesterolemia, colon diverticulosis, appendectomy, histerosalpingo-oophorectomy for benign pathology and left mastectomy and axillary dissection for malignant neoplasm with negative follow-up.
Laboratory examinations on admission revealed a total bilirubin of 4,83 mg/dl (reference range 0,20-1,20), an alanine transaminase of 364 U/l (reference range 2-31), an aspartate transaminase of 191 U/l (reference range 2-31), a C Reactive Protein of 1,86 mg/dl (reference range 0 - 0,7). The other blood data, included neoplastic markers CEA and Ca 19-9 levels, were normal.
On admission the work up included an ultrasound of upper abdomen, an abdominal CT-scan and MRI-MRCP. The ultrasound showed hydropic gallbladder without gallstones, dilatation of common bile duct and intrahepatic biliary tree and diffuse un-homogeneity of the whole pancreas.
The abdominal CT-scan (64 slice VTC LightSpeed Plus, General Electric Medical System, Milwaukee, USA) revealed a heterogeneous mass in the head of the pancreas with maximum transverse diameter of 36 mm, formed by microcystic lesions with wall-enhancement in post-contrast imaging. The mass appeared in contact with duodenal wall and with the superior mesenteric vein, without signs of vascular invasion. CT-scan also highlighted dilatation of main pancreatic duct (9 mm), common bile duct (12.5 mm) at the level of pancreatic head, and of intra-hepatic biliary ducts (4.5 mm) (Fig. 1). It showed no liver nor peritoneal metastases, but detected some retroperitoneal nodes with increased diameter (16 mm).

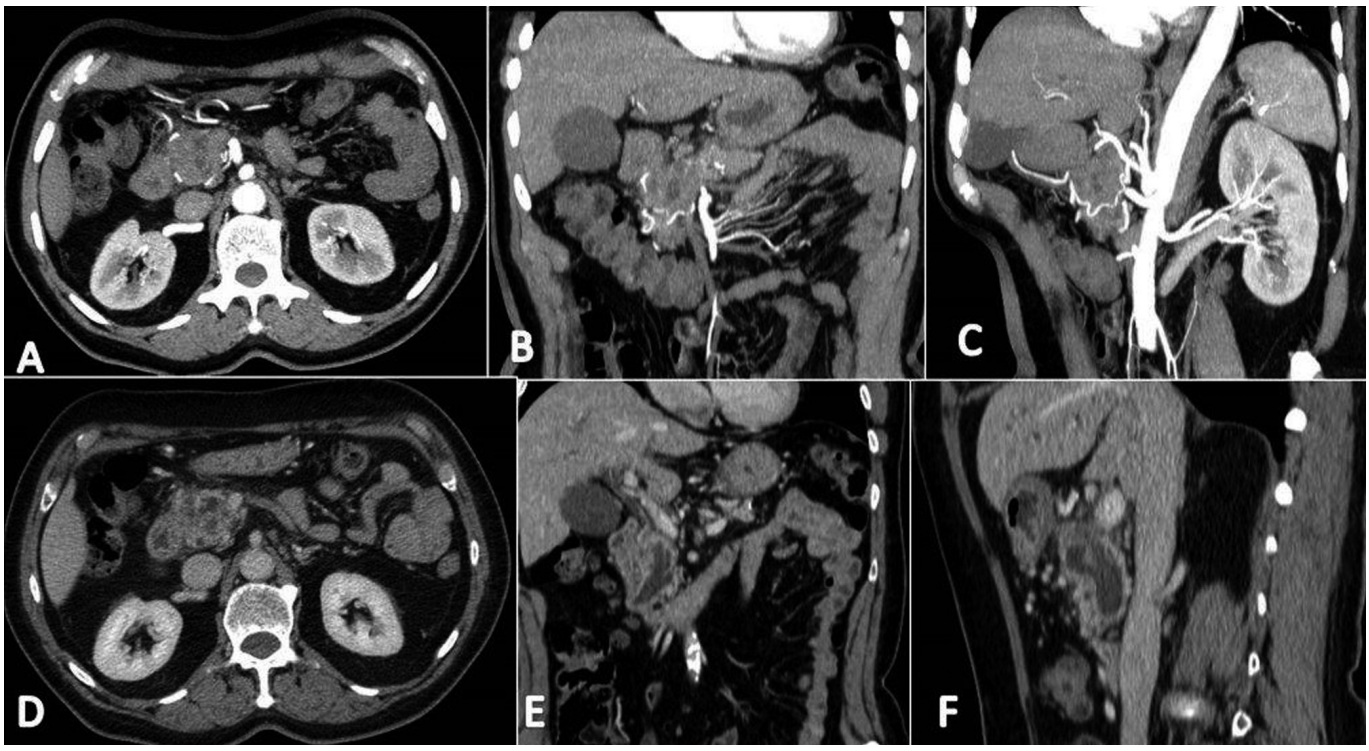

Fig. 1.

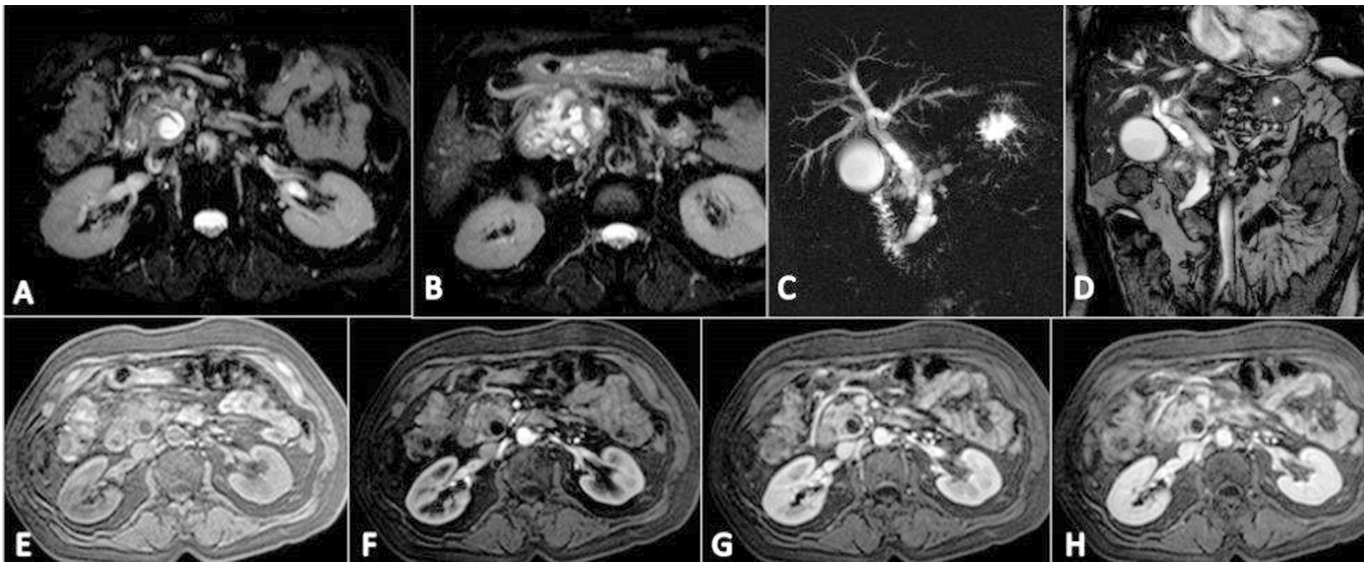

Fig. 2.

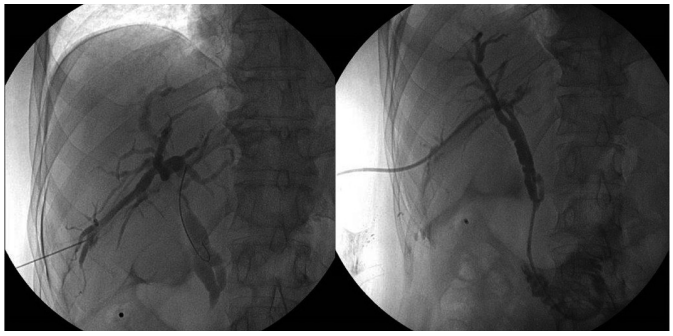

Fig. 3.

MRI-MRCP scan (Achieva 1.5 Tesla, Philips Medical System, Best, The Netherlands) further characterized this lesion demonstrating the communication with a clearly dilated main pancreatic duct, with no evident cause for obstruction revealed (Fig. 2). The imaging findings were suspicious for the diagnosis of Intraductal Papillary Mucinous Tumor (IPMT) and surgical resection was decided.

Because of the progressive bilirubin increasing the patient went on to have ERCP, which showed up to the papilla of Vater a pancreatic mass with a wide orifice and mucinous discharge, but failed in biliary drainage positioning due to the common bile duct stenosis. Targeted biopsies were performed and the histology revealed inflammatory tissue and no evidence of neoplastic cells. A percutaneous transhepatic cholangiography (PTC) and biliary drainage was positioned (Fig. 3) and the patient subsequently underwent a spleen preserving total pancreatectomy. Total pancreatectomy was deemed the most appropriate surgical option due to atrophy of the body and tail of the pancreas which were replaced by fibrotic and abscessual tissue.

Final histology reported an intraductal papillary mucinous carcinoma in situ of the head of the pancreas and an intense chronic and acute inflammatory infiltrate, with abscessual areas and widespread fibrosis of all the remaining pancreatic parenchyma. All nodes (25) examined were negative for metastatic disease.

The patient had an uneventful postoperative course, she was discharged from hospital 10 days after surgery and has a 15 months negative follow-up.

Discussion and Comments

Clinical and diagnostic features of IPMTS

With the improvement of the diagnostic imaging during the last decades, pancreatic cystic lesions are detected with more frequency. Intraductal Papillary Mucinous Tumors (IPMTs) are a recently well-characterized category of neoplasms of the exocrine pancreas with a clear malignant potential. It's not easy to define the real incidence of IPMTs because most of them are completely asymptomatic but, at the moment, IPMTs seem to represent 1-3% of all exocrine pancreatic neoplasms and 20-50% of all cystic neoplasms of the pancreas [5-8].

According to the WHO classification established in 1996, IPMTs are included in the category of pancreatic cystic tumours and defined as mucinous producing neoplasms, with tall, columnar epithelium with or without papillary projections. According to their origin, IPMTs are subcategorized into main duct (MD-IPMT) such as in the case presented, branch duct (BD-IPMT) and mixed type. Based on imaging studies, such as CT or MRCP, the presence of a diffuse or segmental dilatation of the main duct, greater than 5 mm, without oth-

er causes of obstruction, is suggestive for MD-IPMT whereas a pancreatic mucinous cyst in communication with a non expanded main duct suggests a BD-IPMT. This categorization is easier by using more sophisticated imaging techniques (EUS or ERCP) but the most definitive classification is made only by the histologic examination [2,4,9-11].

Most IPMTs are unifocal, 20-30% are multifocal and 5-10% diffusely affect the entire duct system of the pancreas [12,13]. In agreement with their malignant transformation these neoplasms are divided into benign IPMT (with low dysplasia), borderline IPMT (with moderate dysplasia) and malignant non invasive IPMT (with carcinoma in situ) as described above. When there is an invasive component, the tumour is defined as IPMT with an associated invasive carcinoma [6-8, 14-16].

Currently, four subtypes of IPMTs have been characterized: intestinal, pancreato-biliary, oncocyte and gastric type. The first three types originate from the main duct while the gastric one occurs typically in the secondary ducts [7,16].

It has been demonstrated that tumours involving main duct are more associated with malignancy and have a poorer prognosis compare to the others confined to the secondary branches. A malignant tumour, in fact, is found in 6-46% of BD-IPMTs while in 57-92% of MD-IPMTs [7,13,17].

As well as the pancreatic ductal adenocarcinoma, IPMTs seem to follow a defined pattern, progressing from IPMT adenoma, to IPMT borderline, to carcinoma in situ and finally to invasive carcinoma [19].

Over 30% of non invasive IPMTs has the possibility to become invasive and even to metastatize but the progression time is estimated to be in general slow, within about 5-6 years [6,15].

Tumor markers in cystic fluid, have been studied to differentiate between benign and malignant IPMT; there are studies reporting that a level of Carcino-embryonic antigen (CEA) over 200 ng/ml has a sensitivity of 90% and specificity of 71% in differentiating benign and malignant IPMT, while a cystic carbonic anhydrase 19-9 (CA 19.9) over 10.000 U/mL has a sensitivity of 80% and specificity of 50%. Other studies show that neither CEA nor CA 19.9 were useful to distinguish malignant to benign IPMTs. The use of tumor markers is still debated but the identification of atypical cells by cytology in combination of a level of CEA over 2.500 ng/ml seems to be more sensitive than malignant cells alone [7,20-22].

Specific etiology factors for the insurgence of an IPMT are not reported but IPMTs are described in patients with Peutz-Jegher syndrome or with familial adenomatous polyposis.

These tumours are more frequent in men between 60 and 70 years of age and IPMT with invasive carcinoma is found in patients 3-5 years older than patients with non invasive neoplasms. MD-IPMTs are more often symptomatic rather than BD-IPMTs which are usually found incidentally during imaging examinations for other medical indications [7,23-29].

There is not a typical clinical presentation of IPMTs and in 20-30% of cases the patients are completely asymptomatic. When symptomatic most patients describe common general symptoms including nausea, epigastric discomfort, abdominal pain and backache. In some cases the presenting symptomatology resembles that of recurrent pancreatitis or could be present pancreatic exocrine or endocrine insufficiency. The presence of weight loss and jaundice at the diagnosis correlates with the discovering of an invasive IPMT [5,28,30,31]. In the case reported, although present, weight loss and jaundice were related to the localization of the tumour (head of pancreas) and the contemporary chronic pancreatitis.

The differential diagnosis, with the other pancreatic cystic tumours, is of particular importance for the discovering of the potentially malignant lesions and in order to reduce the need for surgery in benign cases. Serous cystic neoplasms are the most common cystic lesions of the pancreas, but only very rarely malignant, therefore surgery is contemplated only for symptomatic or progressive growing lesions. Mucinous cystic neoplasms of the pancreas, affect in more than 90% of cases, women between the 4th and 6th decades of life, are mostly localized in the tail of the pancreas and differ form IPMT for its lacking connection to the duct and presenting ovarian-type stromal component. Surgery is indicated in every case of mucinous cystic neoplasm because of the potential malignancy. Solid papillary tumours are benign in more than 90% of cases and affected mainly young women [31]; there are also pseudocystic lesions of the pancreas which are not easily distinguishable from pancreatic cancer and for the definitive diagnosis surgery is often indicated [1,12,33,34].

Imaging of IPMTS

The role of diagnostic imaging is to discover an IPMT of the pancreas, to exclude other pancreatic cystic neoplasms, to differentiate MD and BD-IPMTs, to predict the presence of malignancy and also the possibility of a complete resection.

Ultrasonography (US) represents the first-line investigation, as it is widely available, non-invasive and allows complete evaluation of the upper abdomen, which is useful also for loco-regional staging of neoplastic masses. However, because of its limitation (meteorism, obesity, operator-dependent) it often must be integrated with second-line investigations, in particular in patients with pancreatic masses [35-37]. In our case, the abdominal US didn't show other than a unhomogeneous whole pancreatic gland in addition to dilated intra and extrahepatic biliary ducts.

CT-scan is the most commonly employed imaging modality for the identification and preoperative staging

of pancreatic malignancies, permitting, in post-contrast acquisition, to evaluate the enhancement of the lesion and its relationship with adjacent vascular structures, crucial for preoperative planning [38]. CT-scan appearance of IPMTs may mimic those of chronic pancreatitis and other cystic pancreatic tumors. However communication with the main duct, location in the head and uncinate process of the pancreas and bulging of the duodenal papilla are features suggestive of IPMT [39,40].

MRI imaging offers optimal contrast resolution for studying the upper abdomen, and with the acquisition of cholangiopancreatography sequences (MRCP-MRI) it depicts the anatomy of bile and pancreatic ducts with high contrast resolution. These sequences are fundamental in the diagnosis of IPMT because permit the demonstration of the communication between the cystic lesion and the main or branch ducts [41] such as in the case presented.

MRI also represents a valid diagnostic alternative to CT-scan in the evaluation of patients with pancreatic masses, offering accurate loco-regional anatomical assessment of both parenchymal and vascular structure with high contrast resolution [38, 39].

IPMTs could be classified into MD, BD-IPMT and mixed type based on imaging studies and/or histology; a dilatation of > 5 mm without other causes of obstructions is diagnostic for a MD-IPMT with and high sensitivity and specificity. The last international guidelines for the management of IPMT established that an asymptomatic pancreatic cyst < 10 mm doesn't need further investigations, while CT or MRI with MRCP is recommended for all pancreatic cysts ≥ 1 cm to better define the lesions. The imaging studies should check for the presence of "worrisome feature" including cyst ≥ 3 cm, thickened enhanced cyst walls, non enhanced mural nodules, abrupt change of the MPD with distal pancreatic atrophy and lymphadenopathy. The presence of MPD ≥ 10 mm, enhanced solid component or obstructive jaundice is defined as "high risk stigmata" and pancreatic cyst presenting these features should be resected [18].

Based on high quality radiological imaging, pancreatic tumors are classified as resectable, locally advanced or metastatic. Tumors of "borderline resectability" are emerging as a distinct subset of pancreatic tumors and do not easily fit the traditional categories of resectable or locally advanced pancreatic cancers [42,43].

According to The American Joint Committee on Cancer (AJCC) TNM (Tumor, Nodes, Metastasis), criteria for resectability include the absence of tumor extension to the celiac artery (CA) and superior mesenteric artery (SMA), a patent superior mesenteric vein (SMV) and portal vein (PV), and no distant metastases (hepatic, extra-abdominal, peritoneum, omentum, lymph nodes outside the resection zone). Locally advanced, surgically unresectable tumors are defined as those that encase the adjacent arteries (celiac axis, SMA, common hepatic artery) or that occlude the SMV, PV, or SMPV confluence [44].

Therapy and Prognosis

Several controversies remain over the treatment of IPMTs especially for the BD-IPMTs. The international guidelines for management of IPMT reported in 2006, and confirmed in 2012, have established that the presence of main duct involvement, clinical symptoms, tumor size > 3 cm, solid changes within IPMT such as "mural nodes" and positive cytology or the presence of CEA in cystic fluid are strong indicators for malignant neoplasm [17].

According to the international guidelines, whereas a pancreatic resection is strongly indicated, if the patient is a good candidate, in every MD-IPMT, the treatment of BD-IPMT is more conservative. The actual accepted indications for pancreatic resection in BD-IPMT are symptoms, suspicious malignant radiological findings, tumor size > 3 cm, main pancreatic dilatation, common bile duct dilatation, lymphadenopathy, rapidly increasing cyst size and high grade atypia at the cytology [7,17,18]. However, the treatment should be individualized, based on patient's preferences and conditions, cyst location and the availability of safe pancreatic resection: BD-IPMT of > 3cm without "high risk stigmata" could be observed without immediate resection and a young patient with a cyst size >2 cm may be candidate for resection owing to the cumulative risk of malignancy [17] .

Typical surgical resection include Whipple's procedure, distal pancreatectomy and total pancreatectomy, based on the site of the disease, with lymph node dissection. Limited resections could be contemplated in very small lesions without any suspected malignant feature and should be always decided during a final intraoperative evaluation. In all cases surgeons must try to achieve negative surgical margins and when a positive margin is present in frozen section examinations, additional resections should be performed until a negative margin is confirmed [5,7,15,45,46].

In the case reported, the patient was scheduled for a Whipple's procedure but even if the frozen section of the resection margin was negative for, because of the atrophy of the body and tail of the pancreas which were replaced by fibrotic and abscessual tissue, intraoperatively we have decided to perform a spleen preserving total pancreasectomy plus lymph node dissection.

For the non surgical BD-IPMT cases the risk for the insurgence of pancreatic adenocarcinoma is higher than normal population and an imaging surveillance of lesions should be considered.

The follow-up should provide information about the size and the communication with the main duct of the tumor and the presence of solid elements. Follow-up could be performed with CT-scan or MRCP and should be every 2-3 years for lesions < 1 cm, every year for 1-2 cm lesions, every 3-6 months for 2-3 cm tumors and for cysts greater than 3 cm. In these two last cases surgery could be contemplated in young fit patients [17,18].

Also patients with resected benign IPMTs have a risk of

recurrence in the remaining pancreas and therefore they can benefits from further resection if it happens. The recurrence rate and its relationship to surgical margins is not clear but seems to be at least 7% in non-invasive IPMTs [12]. The follow-up strategy for resected IPMT depends on the eventual presence of IPMT in the remnant pancreas and on resection margin status; if there are no residual lesions and the margins are negative, examinations at 2 and 5 years may be reasonable to check for new recurrence. The recurrence rate in invasive IPMTs, instead, is significantly high and therefore a follow-up strategy identical to that for pancreatic adenocarcinoma is recommended [17,18].
The prognosis depends on the presence of an invasive carcinoma even if, compare to the ductal adenocarcinoma, IPMTs have a better prognosis: in resected cases the 5 years survival rate is of 90% for non invasive neoplasms and of 40%-60% for the invasive forms [47-49].

Conclusions

Our report describes the case of a non invasive MD-IPMT of the pancreas with clinical symptoms and radiological findings typical of an invasive pancreatic tumor arose in a recurrent mild pancreatitis. The abdominal CT-scan posed many doubts about the nature of the pancreatic mass and also about the resectability of the tumor. The biopsies performed during ERCP were negative for the presence of neoplastic cells. Performing a MRCP the hypothesis of IPMT was considered even if the diagnosis wasn't definitive and the possibility of a potential curative surgery was contemplated. The patient underwent a spleen preserving total pancreatectomy and had a complete resection of a MD- IPMT with carcinoma in situ without any complications and with 15 months negative follow-up.
IPMTs are cystic tumours of the pancreas that are increasingly diagnosed but often pose difficult differential diagnosis. The treatment should be individualized according to international guidelines but at the moment a better understanding of the natural history of these neoplasms is needed to refine them. The patients with a suspected diagnosis of IPMT, should be investigated by US, CT and MR imaging and the execution of an ERCP with brush cytology could often be very helpful. The resectability and the absence of an invasive carcinoma are the most important prognostic factors and a radical resection is crucial to reduce the recurrence rate. During surgery, the dysplastic epithelium should be completely removed even if a total pancreatectomy is required. For this reason, the imaging modalities are very important to pose the right diagnosis of IPMT when suspected and must be chosen for the preoperative evaluation to maximise the chance to select the right surgical candidate and to perform the best treatment for each patient.

Riassunto

Le lesioni cistiche del pancreas costituiscono un ampio spettro di entità tra le quali alcune benigne e altre potenzialmente maligne come le cisti mucinose e i tumori intraduttali papillari (IPMT).
Una corretta identificazione e caratterizzazione delle lesioni cistiche pancreatiche è necessaria per stabilire il corretto approccio terapeutico, ma spesso risulta complessa, a causa di una sovrapposizione di caratteristiche morfologiche delle differenti lesioni alle indagini di routine.
Presentiamo il caso di una donna caucasica di 68 anni ricoverata nella nostra unità in seguito alla comparsa di dolore epigastrico, irradiato a sbarra, ingravescente da circa 3 mesi, associato a nausea, perdita di peso, disfagia progressiva, ittero ostruttivo, in una storia recente di dolori addominali ricorrenti.
La valutazione clinica, l'ecografia addominale e la TC addome ponevano il sospetto di adenocarcinoma con degenerazione cistica o di un cistoadenocarcinoma mucinoso della testa pancreatica. Le scansioni MRI-MRCP, dimostrando una chiara comunicazione della lesione con il dotto pancreatico principale marcatamente dilatato, ponevano la diagnosi differenziale tra un IPMT e un cistoadenocarcinoma mucinoso. L'ERCP mostrava una lesione a carico del duodeno dalla quale fuoriusciva materiale mucoide e, le biopsie mirate eseguite, non evidenziavano presenza di cellule neoplastiche.
La paziente è stata candidata ad intervento chirurgico secondo Whipple, ma per il riscontro di atrofia e tessuto ascessuale a carico di tutto il corpo-coda pancreatico, in corso di intervento, si decideva di eseguire una pancreasectomia totale con risparmio della milza.
L'esame istologico definitivo mostrava un IPMT con carcinoma in situ della testa pancreatica.
La paziente ha avuto un decorso postoperatorio regolare, dimessa in decima giornata post-opeatoria con un attuale follow-up negativo di 15 mesi.
I tumori mucinosi intraduttali del pancreas, secondo la classificazione WHO del 1996, sono definiti come neoplasie a produzione mucinosa, con epitelio colonnare alto, con o senza proiezioni papillari.
In accordo alla loro origine vengono distinti in IPMT del dotto principale (MD-IPMT), dei dotti secondari (BD-IPMT) o di tipo misto. In base alla loro trasformazione maligna, gli IPMT si distinguono in IPMT benigni, borderline, maligni non invasivi (carcinoma in situ) e maligni associati a carcinoma invasivo.
All'esordio i sintomi sono generali e del tutto aspecifici, includono nausea, epigastralgia, dolore a sbarra e a volte possono ricordare la sintomatologia di una pancreatite cronica. La perdita di peso e l'ittero alla diagnosi correlano con il riscontro di un IPMT invasivo.
L'ecografia addominale rappresenta l'indagine di primo livello più utilizzata, ma generalmente, deve essere integrata con indagini di secondo livello, come la TC ma soprattutto la MRCP-MRI che permette di evidenziare

la comunicazione esistente tra la lesione cistica e i dotti pancreatici, patognomonica di un IPMT.
Nel trattamento degli IPMT rimangono ancora delle controversie, specialmente per quanto riguarda i BD-IPMT e le linee guida internazionali del 2012 hanno stabilito che, se in ogni MD-IPMT la resezione chirurgica è fortemente raccomandata, per i BD-IPMT il trattamento dovrebbe essere individualizzato e la resezione chirurgica dovrebbe essere considerata solo nei casi sospetti per malignità.
La prognosi e le recidive dell'IPMT dipendono sia dalla radicalità chirurgica che dalla presenza di carcinoma invasivo; per questo il ruolo della diagnostica per immagini è di cruciale importanza nella diagnosi differenziale ma soprattutto per individuare i pazienti chirurgici e per ottimizzare le opzioni terapeutiche in ogni singolo paziente.

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