Multifocal intraductal papillary mucinous neoplasm of the pancreas from mild dysplasia to invasive carcinoma
A case report

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Multifocal intraductal papillary mucinous neoplasm of the pancreas from mild dysplasia to invasive carcinoma. A case report

Intraductal papillary mucinous neoplasm (IPMN) is defined as an intraductal mucin-producing neoplasm of the pancreatic ducts. IPMNs may be multifocal, have malignant potential and exhibit a broad histological spectrum ranging from adenoma to invasive carcinoma. The "hyperplasia-dysplasia-carcinoma sequence" in the evolution of IPMNs is considered very similar to the "adenoma-carcinoma sequence" of colorectal tumours. Patients with multifocal IPMN are potential candidates to total pancreatectomy, which still carries significant perioperative risks, especially in the elderly. In selected cases a reasonable alternative to total pancreatectomy is represented by the resection of the dominant tumour leaving deliberately in place the smaller, low-risk tumours. In this context, intraoperative ultrasonography (IOUS) can be useful to define the extent of IPMNs and to plan the surgical strategy.
We report the case of a 84-year-old female with multiple IPMNs showing different stages of neoplastic progression up to invasive carcinoma. The patient underwent IOUS-guided distal splenopancreatectomy, while the small multiple branch-duct type IPMNs of the head of the pancreas were considered at very low risk of neoplastic progression and were deliberately left in place. The patient is alive without recurrence 96 months after surgery and without evidence of progression of the branch-duct type IPMNs of the head of the pancreas.
IOUS-guided pancreatectomy should be considered in selected elderly patients affected by multifocal IPMN evolved to invasive carcinoma without evidence of distant metastases.

KEY WORDS: Intraductal papillary mucinous neoplasm, Intraoperative ultrasonography, Pancreatectomy

Introduction

Intraductal papillary mucinous neoplasm (IPMN) has been first recognized as a distinct entity in 1982 [1]. According to the WHO classification, IPMN is defined as an intraductal mucin-producing neoplasm of the main pancreatic duct and/or side branches, with variable degrees of papillary formation, mucin production, and cystic dilation [2]. IPMNs may be multifocal, have clear malignant potential and exhibit a broad histological spectrum ranging from adenoma to invasive carcinoma [3,4]. Neoplastic progression is usually slow, thus showing a spectrum of neoplastic transformations, with some histotypes of invasive carcinoma being characterized by a more favourable prognosis than pancreatic ductal adenocarcinoma (PDAC) [3,4].
It is well known that some carcinomas arise from their precursor lesions as a result of the mutational activation of oncogenes coupled with the inactivation of tumour

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suppressor genes; there is convincing evidence that the "hyperplasia-dysplasia-carcinoma sequence" in the evolution of IPMNs is very similar to the "adenoma-carcinoma sequence" of colorectal tumours [5]. It has been hypothesized that IPMNs are mostly poly or oligoclonal in origin [6,7], and that a field multicentric cancerization, resulting from the fusion of two or more independent monoclonal precursor lesions, might be the basis of IPMN development [6,8].

IPMN is diagnosed mostly in the seventh decade. Pancreatic surgery is traditionally considered at risk in elderly patients. However even selected, otherwise healthy patients 80 years of age and older are eligible for pancreatic resection with perioperative and long-term results approaching those observed in younger patients [9,10]. Patients with multifocal IPMN are potential candidates to total pancreatectomy, which however still carries significant perioperative risks and results in definitive endocrine and exocrine insufficiency [1]. In selected cases a reasonable alternative to total pancreatectomy is represented by the resection of the dominant tumour leaving deliberately in place the smaller, low-risk tumours [1,11]. In this context, intraoperative ultrasonography (IOUS) can be useful to define the site and extent of IPMNs and to plan the surgical strategy [12-14].

We report the case of an elderly patient with multiple IPMNs showing different stages of neoplastic progression up to invasive carcinoma who underwent IOUS-guided distal splenopancreatectomy.

Case Report

A 84-year-old white woman presented in November 2006 with abdominal discomfort and weight loss of 12 kg within 6 months. She denied other relevant clinical symptoms. No exocrine pancreatic insufficiency was noted. Persistent slight hyperglicemia had appeared in the last few months. Her medical history revealed hypertension and well compensated ischemic heart disease.

The esophagogastroduodenoscopy and a barium enema had excluded the presence of malignant tumours of the upper gastrointestinal tract and of the large intestine. The CT scan of the abdomen showed a solid mass of the tail of the pancreas infiltrating the splenic vessels; multiple branch-duct type IPMNs were evident in the head and the body of the pancreas with a slight dilatation of the main duct; a 20-mm IPMN was present at the isthmus of the gland (Fig. 1). There was no evidence of nodal or distant metastases. Endoscopic ultrasound confirmed the diagnosis of multifocal IMPN of the whole pancreas; fine needle aspiration of the solid mass revealed the presence of malignant cells. Tumour markers carcinoembryonic antigen and carbohydrate antigen 19-9 were 9.1 ng/mL (normal ranges 0 to 4.6 ng/mL) and 720 U/mL (normal ranges 0 to 39 U/mL), respectively. After diagnostic work-up, the patient was admitted to our unit.

Since the small multiple branch-duct type IPMNs of the head of the pancreas were considered at very low risk

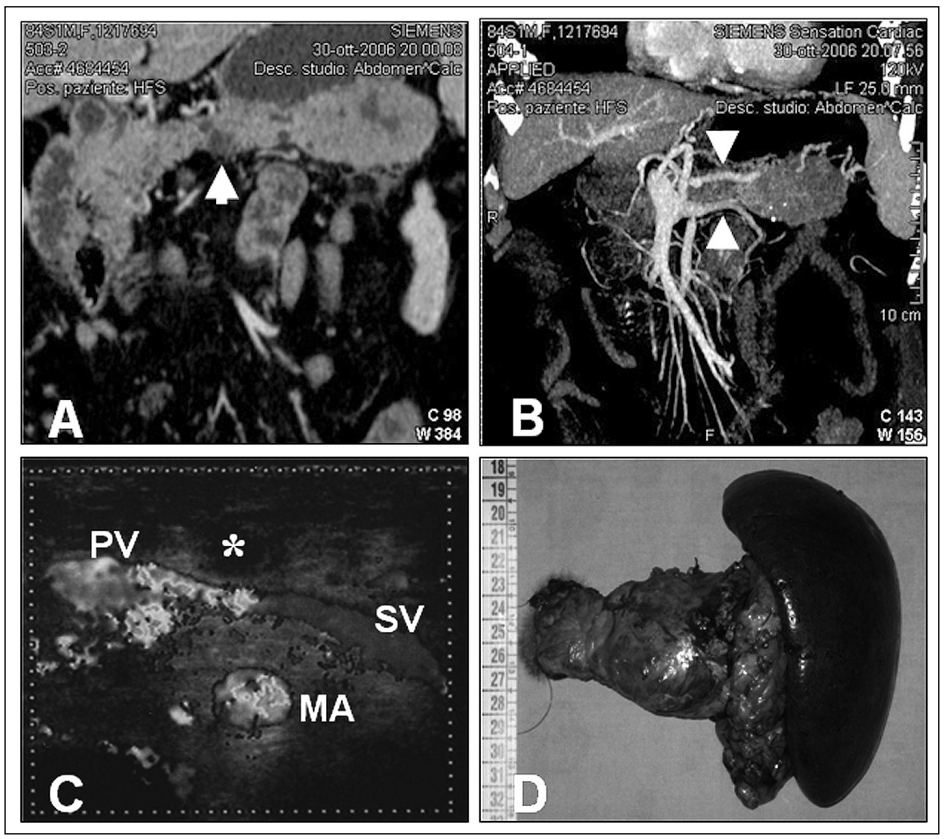

Fig. 1: A,B) At the CT scan of the pancreas a 20 mm IPMN is evident in the isthmus of the pancreas (arrow), corresponding to noninvasive carcinoma on pathologic examination of the specimen of distal pancreatectomy (A); the invasive carcinoma at the tail of the pancreas infiltrates the splenic vessels (arrowheads) (B). C) Intraoperative ultrasonography was used to define the resection margin and permitted to include in the specimen the 20-mm cystic neoplasm of the isthmus (asterisk). MA: mesenteric artery; PV: portal vein; SV: splenic vein. D) Specimen of the distal pancreatectomy.

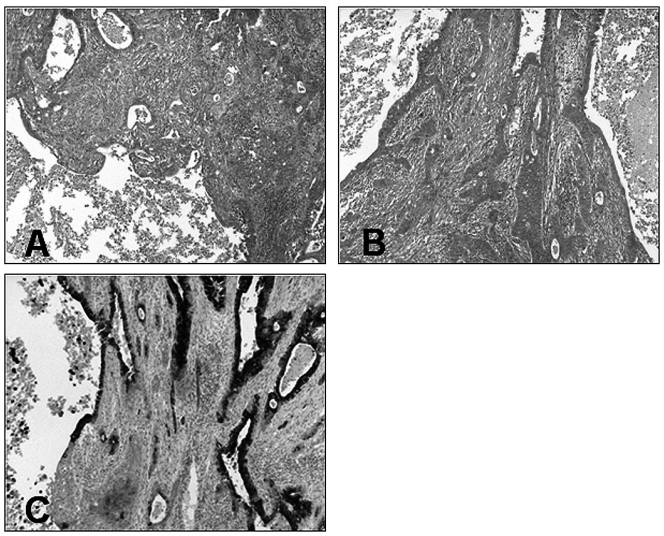

Fig. 2: Histological and immunohistochemical features of the invasive carcinoma of the tail of the pancreas. Areas of pancreatobiliary-type, moderately differentiated invasive adenocarcinoma (A,B) (hematoxylin-eosin stain, x20), overexpressing cytocheratine 7 (C) (CK7 immunoistochemical stain, x20).

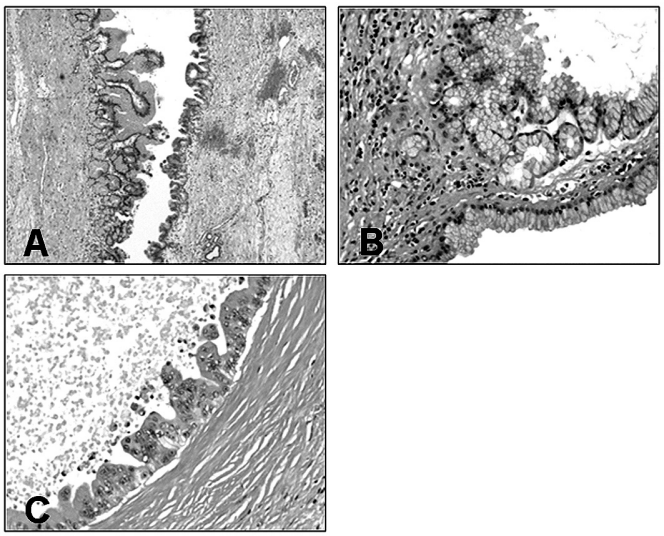

Fig. 3: Histological features of the cystic tumour of the isthmus of the pancreas. Gastric-type IPMN, with areas of low-grade dysplasia (A, B) and high-grade dysplasia/*in-situ* carcinoma (C) (hematoxylin-eosin stain, x10; x20; x40).

of neoplastic progression and we were reluctant to perform total pancreatectomy in a 84-year-old patient, distal splenopancreatectomy was planned. The IOUS examination confirmed the preoperative findings of multiple cystic lesions of the whole pancreas and the large cancer of the pancreatic tail infiltrating the splenic vessels, without evidence of nodal metastases. IOUS was used to define the resection margin and permitted to include in the specimen the 20-mm cystic neoplasm of the isthmus (Fig. 1). The pancreatic margin was negative for invasive tumour on frozen section analysis. The postoperative course was complicated by a bacterial pneumonia which remitted with antibiotics and the patient was discharged on 24th postoperative day.

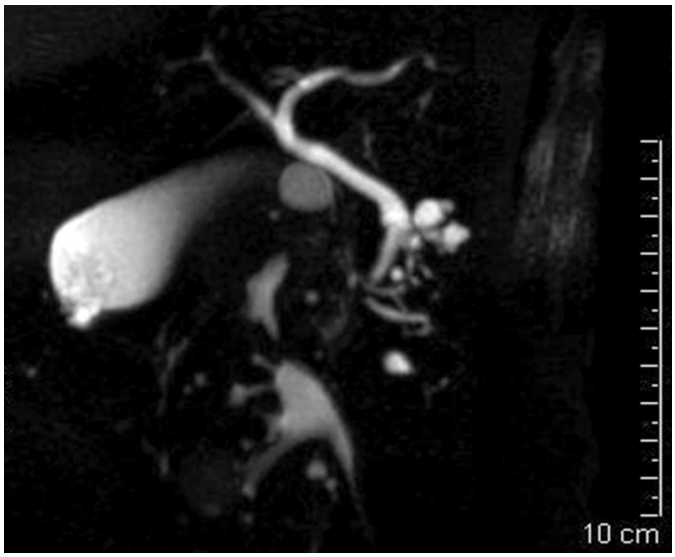

Fig. 4: MRCP of the head of the pancreas 42 months after pancreatic resection. The residual branch-duct type IPMN measures 13 mm without dilatation of the main duct and without evidence of progression.

Pathological examination showed an invasive, moderately differentiated carcinoma of the tail of the pancreas (Fig. 2) without evidence of regional nodal metastases; multifocal IPMN was evident in the remaining tissue, with broad histologic spectrum ranging from dysplasia to noninvasive carcinoma: the 20-mm cystic neoplasm of the isthmus near the resection margin was a IPMN containing foci of noninvasive carcinoma (Fig. 3). The pancreatic margin was negative for invasive tumour but contained foci of low-grade dysplasia.

The patient is in excellent conditions without recurrence 96 months after surgery. The seriated controls with helical CT scans and MR cholangiopancreatography show that the branch-duct type IPMN of the head of the pancreas measures 13 mm without evidence of progression and without dilatation of the main duct (Fig. 4).

Discussion

IPMNs are intraductal mucin-producing tumours of the pancreatic ducts with unique clinicopathological features, characterized by variable degrees of papillary formation, mucin production, and cystic dilation [2]. Multifocal occurrence of IPMNs in the same pancreas is also peculiar [3,4]. IPMNs have malignant potential and are divided, according to the degree of cytoarchitectural atypia,

into adenoma or low-grade dysplasia, borderline or moderate dysplasia, *in-situ* carcinoma or high-grade dysplasia and invasive carcinoma [2]. These histologic varieties within IPMNs support the concept of "clonal progression" in the evolution of these tumours and are considered similar to the "adenoma-carcinoma sequence" of colorectal neoplasms and pancreatic ductal adenocarcinoma. Invasive carcinoma derived from IPMN is classified as an invasive adenocarcinoma originating in an IPMN, i.e. showing either gross or histological evidence of a preexisting IPMN, even though a conventional PDAC may develop independently, as a separate tumour concomitant with IPMN [3,4]. The histotype of invasive carcinoma derived from IPMN has important prognostic implications, with the colloid carcinomas having a less aggressive biological behaviour and a better outcome after surgical resection than tubular cacinomas [3,4]. The recurrence rate after pancreatic resection of invasive branch-duct and main-duct IPMNs varies in the different series but occur in at least 50% of patients [15].

There is growing evidence that the majority of IPMNs are poly or oligoclonal in origin, leading to the conclusion that a field multicentric cancerization, resulting from the fusion of two or more independent monoclonal precursor lesions, might be the basis of IPMN development [6,8]. Genetic abnormalities have been detected either in IPMNs or in morphologically normal duct epithelium lining areas of mucinous hyperplasia adjacent to IPMNs [7]. Hence, IPMNs are not clearly delineated but rather surrounded by areas containing a mixed population of epithelial cells with or without genetic aberrations [8]. Similarly, multiple distinct genomic alterations have been identified among different hyperplasias in half of the patients with PDAC [16], adding molecular support for field multicentric cancerization also for PDAC. The same mechanisms might explain the occurrence of synchronous but topographically separate PDAC or metachronous PDAC in patients followed-up for branch-duct IPMN [17]. IPMNs are therefore not only precursor lesions of invasive carcinoma but also markers of a global disorder of the duct epithelium leading to higher risk of carcinogenesis. In this patient we had the unique opportunity to observe different IPMNs in different steps of carcinogenesis, with multiple concomitant cystic tumours showing different grades of dysplasia, a noninvasive cancer within the 20-mm tumour near the resection line, and an invasive carcinoma without nodal involvement at the tail of the pancreas. These findings support the hypothesis that a global field defect could be the basis of multicentricity of branch-duct IPMNs in some patients.

IPMN is diagnosed mostly in the seventh decade, so that the indication to surgical resection has usually to face with significant surgical risks. In general, candidates to total pancreatectomy or pancreaticoduodenectomy for IPMN are still at risk of postoperative death or significant complications [18]. More limited pancreatectomies including distal and medial pancreatectomy, limited resections of the pancreatic head, enucleation, have lower mortality rates even if the incidence of postoperative complications remains quite high [1]. Even though pancreatic surgery in the elderly is traditionally considered hazardous, recent studies have shown that pancreatic resections can be safely performed in adequately selected elderly patients, with mortality rates usually below 10% and perioperative complication rates comparable to those observed in younger patients [9]. Even selected, otherwise healthy patients 80 years of age and older have been successfully considered for potentially curative resection of pancreatic tumours [10].

Patients with multifocal IPMN are potential candidates to total pancreatectomy, which however still carries a significant risk of postoperative mortality and results in definitive exocrine and endocrine insufficiency. Diabetes following total pancreatectomy may result in severe metabolic disorders sometimes responsible of frequent rehospitalisation and even death [1,20]. For these reasons, a total pancreatectomy should be limited to selected patients with diffuse main duct IPMN [1] and to a minority of patients with multifocal side branch IPMN, especially in the presence of symptoms or when an extensive/diffuse multifocal disease makes difficult to effectively perform remnant pancreas surveillance [21]. The global risks of total pancreatectomy should be especially addressed in patients 80 years of age and older. In selected patients with multifocal IPMN, particularly the elderly, a reasonable alternative to total pancreatectomy is represented by the resection of the dominant tumour leaving deliberately in place the smaller, low-risk tumours [1,11]. Also a resection margin bearing low-grade IPMN after pancreatectomy for a known invasive adenocarcinoma is not an indication to extend pancreatic resection since the long-term outcome is mainly affected by the invasive tumour and recurrences are usually distant [1,21].

The routine use of IOUS to plan the surgical strategy and to define the resection margin has been demonstrated to be of paramount importance to pursue conservative liver resections for malignant liver tumours [22]. The role of IOUS in the intraoperative management of cystic lesions of the pancreas has been delineated in the past [12], especially in candidates to pancreatic resection for IPMN [13,14]: in this setting IOUS has been proven to be useful for accurate diagnosis of the extent of IPMN and for planning surgical strategy. In our patient a thorough ultrasonographic examination of the parenchyma was conducted and a distal pancreatectomy leaving in place the small IPMN of the pancreatic head was preferred to avoid the unfavourable metabolic consequences of total pancreatectomy. IOUS allowed us to include in the pancreatic stump the 20-mm IPMN of the isthmus containing a noninvasive carcinoma at histology, confirming its value in pursuing radical resection.

In conclusion, the occurrence of multiple IPMNs showing different stages of neoplastic progression up to inva-

sive carcinoma in a single patient confirms that IPMNs may progress through the "hyperplasia-dysplasia-carcinoma sequence" and that multicentric or "field" cancerization may represent the basis of IPMN development. Elderly patient with pancreatic cancer may be adequate candidates to pancreatic resection. Tailored, IOUS-guided pancreatectomy should be considered in selected elderly patients affected by multifocal IPMN evolved to invasive carcinoma without evidence of distant metastases.

Riassunto

La neoplasia papillare mucinosa intraduttale (IPMN) è una neoplasia secernente mucina che insorge all'interno dei dotti pancreatici. Può essere multifocale ed è dotata di potenziale malignità, con uno spettro di caratteristiche istologiche variabile dall'adenoma al carcinoma invasivo. La "sequenza iperplasia-displasia-carcinoma" nell'evoluzione dell'IPMN è considerata molto simile alla "sequenza adenoma-carcinoma" dei tumori colorettali. I pazienti affetti da un'IPMN multifocale sono potenziali candidati ad una pancreasectomia totale, che tuttavia è gravata da significativi rischi perioperatori, specialmente nei pazienti anziani. In casi selezionati, una possibile alternativa alla pancreasectomia totale è rappresentata dalla resezione del tumore "dominante", lasciando deliberatamente in sede le neoplasie di più piccole dimensioni ed a basso rischio. In questo contesto l'ecografia intraoperatoria (IOUS) può essere utile per definire l'estensione dell'IPMN e per pianificare la strategia chirurgica.
Viene riferito il caso di una donna di 84 anni affetta da un'IPMN multifocale in stadi differenti di progressione neoplastica fino al carcinoma. La paziente è stata sottoposta ad una splenopancreasectomia distale IOUS-guidata lasciando deliberatamente in sede le IPMN di tipo II situate nella testa del pancreas. La paziente è vivente a distanza di 96 mesi dall'intervento chirurgico senza evidenza di recidive tumorali né di progressione delle IPMN della testa del pancreas.
In conclusione, le pancreasectomie "tailored" IOUS-guidate andrebbero prese in considerazione anche in pazienti anziani adeguatamente selezionati affetti da IPMN multifocale evoluta verso una neoplasia maligna senza evidenza di metastasi a distanza.

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ERRATA CORRIGE

Nel lavoro Gossetti, et al: «New "all-in-one" device for mesh plug hernioplasty: the Trabucco repair», pubblicato nel n. 6/2015 di Annali Italiani di Chirurgia ci sono tre errori che debbono essere così corretti:

– nel riassunto in inglese alla 5ª e 6ª riga invece di "Plug and Patch" devesi leggere *"Plug & Patch"*

– nella leggenda della figura n. 5 deve essere inserita la parola "synthetic" prima di glue e quindi devesi leggere la frase come *"Some drops of synthetic glue fix the device"*

– nella tabella I in corrispondenza alla colonna "30 days" alla voce VAS al valore 0 devesi leggere *98* invece di 8.

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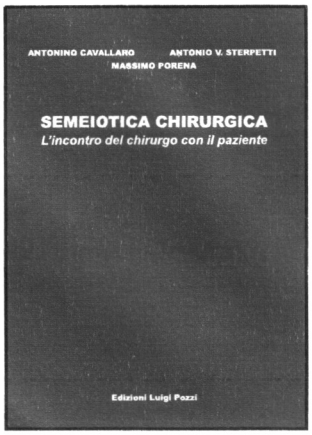

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