



Disease Free Long Survival after Stump Recurrence and Reoperation of Pancreatic IPMN with Invasive Carcinoma

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Abstract

Re-operation on malignant tumours of the pancreatic stump remaining from a previous resection for cancer is very rare. The literature reports few cases in which the tumours were mostly made up of Intraductal Papillary Mucinous Neoplasm (IPMN) sometimes associated with invasive carcinoma or adenocarcinoma (PDAC).

One of those rare cases has come to our attention: a 62 year old man, anicteric, with a massive tumour of the head of the pancreas 11 cm x 7 cm x 5 cm, subjected to DCP for IPMN-MD with isolated areas of invasive cancer, misinterpreted at the beginning as PDAC. Nine years later, with markers remaining negative, it was re-operated on, a total Pancreatectomy for recurrence of the same cancer of the pancreatic stump, despite negative lymph nodes. 15 years after the first surgery and 6 years after the second operation the patient is alive, healthy, diabetic, but the disease free.

The case is an opportunity, through a literature review, to discuss the biological, epidemiological, therapeutic and prognostic differences between invasive carcinoma, developed on intraductal papillary mucinous tumours, and tubular primitive pancreatic adenocarcinoma.

Introduction

Cancer of the pancreas is currently the fourth leading cause of death from cancer, and is in clearly increasing in incidence in both the US and Europe. Despite advances in diagnosis and treatment, only 4% of cases survive 5 years [1]. Unfortunately, over 80% of cases are presented in the advanced stages, and are therefore not resectable.

Surgery is the only chance of recovery, but the 5-year survival in different clinical records varies around 5% [2]. In most cases (80%) the tumour relapses within two years [3]. The median survival varies from 11 months after surgery alone, to 20 months after surgery plus chemotherapy [4]. Relapse occurs primarily in the operating region (65%), lymph nodes (17%), liver (11%), in the peritoneum (7%), with prevalence at the origin of the superior mesenteric artery [5].

The return of the disease on the residual pancreas is rare [6] and in literature only 14 individual cases are traceable, some of which are considered true relapses and some which are interpreted as new primitives.

It should also be noted that, regarding pancreatic cancer, there are several histologic types, no fewer than 13 according to the American College of Pathologists 2005, reported by Lopez [7]. Excluding neuroendocrine forms, adenocarcinoma or ductal carcinoma is the most common and may originate as such, as a primitive pancreatic cancer (PDAC), or occupy an intraductal papillary mucinous neoplasm (Inv-IPMN). These last forms have a better prognosis.

Case Report

V.R. 61 years of age, retired, no precedent of diseases or trauma, or surgery, except exanthematous childhood diseases.

He was hospitalised on 10/12/2001, at the Division of Digestive Surgery of the Regina Elena National Cancer Institute in Rome, for weight loss and dyspepsia, without jaundice, attributable via ultrasound and CT scan (Figure 1) to pancreatic head cancer: "Bulky expansive mass starting at the head of the pancreas with dimensions of approximately 11 cm x 7 cm x 5 cm; the lesion is

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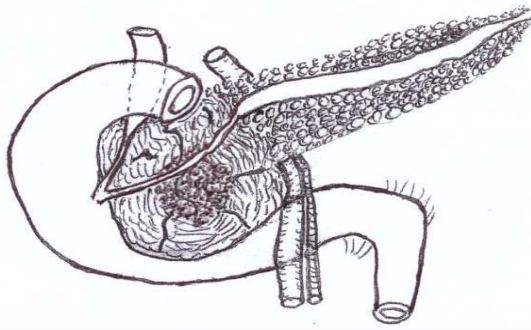


Figure 1: 2001- Pancreatic head bulky expansive mass.

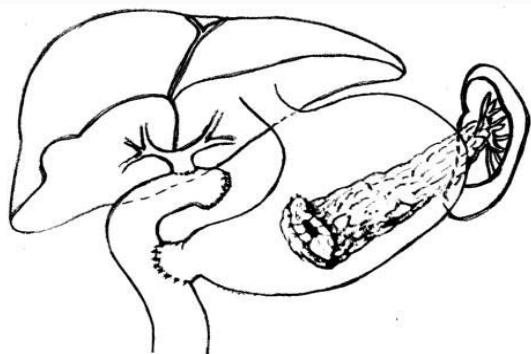


Figure 2: 2001 - DCP pylorus preserving and pancreatico-gastro-anastomosis.

septate with large area of necrosis and with marked contrast graphic impregnation of the walls. Marked dilatation of duct of Wirsung at the body-tail section. The common bile duct has mild ectasia in the distal end and ending in the mass. The lesion has a broad grip with respect to the gallbladder, gastric antrum, the I and II portions of the duodenum, the inferior vena cava, the superior mesenteric vein. Small intraaortocaval lymph nodes are present".

At the clinical examination he was found to be a man of medium height, in a good state of nutrition, not obese, toned, of olive complexion, with no symptoms of disease other than the abdominal palpation of a distended gallbladder, hardly painful. MRI confirmed the CT report. The laboratory tests showed: Hb 13.9 g/dl, GR. 4.850.000, GB 12.100, INR 1.03, Fibrinogen 408 mg/dl, Blood sugar 151 mg/dl, Azotemia 27 mg/dl, Bilirubin 0.36 mg/dl, GOT 10 UI/L, GTP 30 UI/L, Proteinemia 5.6 g/dl, CEA 1.8 ng/ml, CA 19-9 12.4 U/ml.

He was operated on the 12/12/2001 (Prof. Eugenio Santoro): Bilateral subcostal incision. voluminous mass of the head of the pancreas (8 cm x 5 cm) without liver metastasis or peritoneal carcinomatosis. The mass is tense and elastic, mobile on the back surfaces, without evident regional lymphadenopathy.

Proceeded to pancreaticoduodenectomy, Whipple procedure, with cholecystectomy and preservation of the pylorus-duodenal complex. Lymphadenectomy of the hepatic pedicle and the tripod. Frozen sections of the lymph nodes and slices of section of the bile duct and the pancreatic remnant tail: all negative. Reconstruction according to Traverso-Longmire procedure with duodeno-jejunal anastomosis. Roux-en-Y biliary-jejunal anastomosis. Pancreatic-gastric anastomosis on the posterior wall of the stomach in two

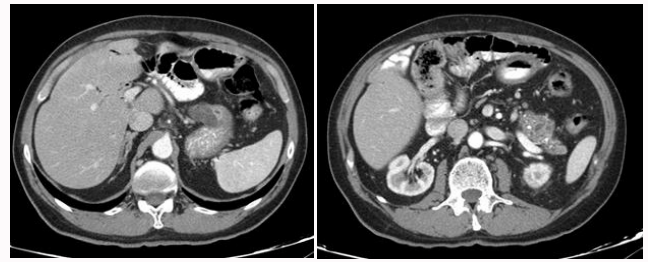


Figure 3: 2008 - Postoperative negative CTscan.

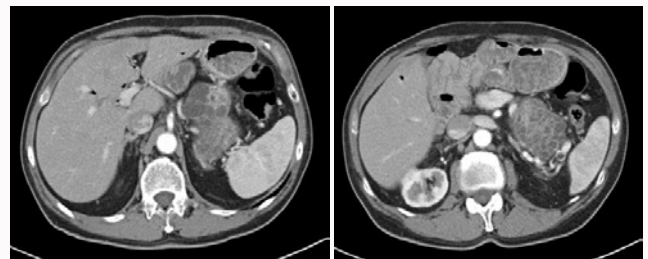


Figure 4: 2010 - Pancreatic remnant mass.

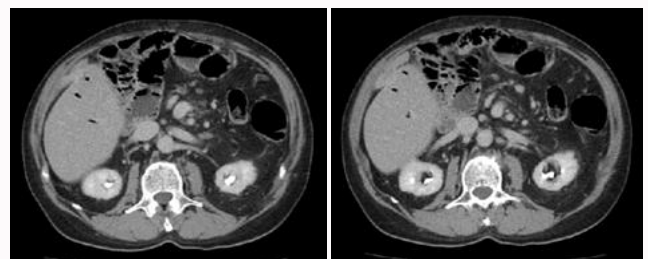


Figure 5: 2016 - Final negative CTscan after total pancreatectomy.

layers of which the inner Wirsung-mucous one had separate stitches (Figure 2). The postoperative course was complicated by high fevers and kidney failure, but was cured medically.

In the months and years that followed the patient presented the same diabetes present at the time of the intervention, sensitive to insulin. Maintained body weight and regular eating and bowel habits. The half-yearly laboratory tests checks-ups were normal, including CEA and CA19-9 markers (Figure 3). Ultrasound and CT scan were negative for disease progression or return (Figure 3) with evidence of calcification and focal ectasia in the residual stump Six years later, in December 2007, he had a sudden melena with severe anaemia and unconsciousness. He was hospitalised on 21/12/2008 Ospedale di Santo Spirito in Rome where he underwent blood transfusions, TPN and fasting. During the gastroduodenoscopy a duodenal ulcer was revealed as the site of the bleeding, on which hemostasis was performed, and also a "evaluation of a gastric lesion 3x4cm with minimal non-mucous area on the posterior wall" that the histological examination of the biopsies showed high grade epithelial dysplasia foci (carcinoma in situ?).

In 2009-2010 subsequent gastroscopies and EUS revealed an unchanged picture. CEA and CA 19-9 markers negative.

In April 2010 a further gastroscopy with EUS highlighted a "solid lump on the back midgastric wall with a diameter of 19mm, occupying mucosa and submucosa with the presence of a central orifice which emits clear liquid". Histological examination of a biopsy

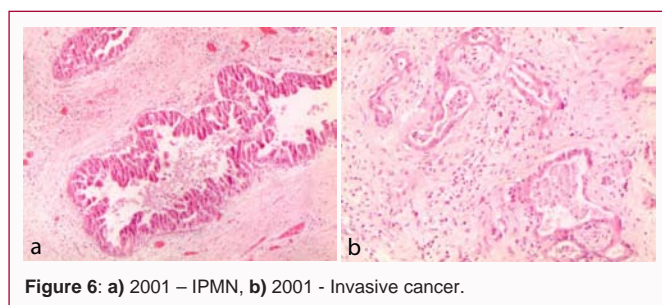


Figure 6: a) 2001 – IPMN, b) 2001 - Invasive cancer.

fragment presumptively showed adenocarcinoma of gastric origin.

He was hospitalised in the Department of General Surgery at the Ospedale Cristo Re in Rome on 21/06/2010. The abdominal CT scan with contrast revealed "... outcomes of pancreaticoduodenectomy with pancreatic-gastric anastomosis. Aerobilia... Irregular increase in size of the residual pancreas, structurally altered by multiple cystic lesions and calcifications... Celiac paraortic and paracaval adenopathies".

On 23/06/2010, 8 and a half years after the first operation, a new laparotomy was carried out on the previous incision"... Viscerolysis, liver end peritoneum disease free... in the retrogastric evidence of increased consistency of the pancreas body-tail particularly in the vicinity of the anastomosis with the stomach. Resection of the blocking anastomotic mass: wide portion of the rear gastric wall, the entire pancreatic stump and spleen. Closure of gastric breach. No evidence of adenopathy" Histological examination of the surgical specimen describes an "adenocarcinoma of the pancreatic stump infiltrating the gastric wall and perivisceral adipose tissue. Lymph nodes unharmed". Simple postoperative course, with early discharge and return to normal life with progressive full physical recovery, normal diet, good appetite, stable body weight, suited to body structure and age, insulin-dependent diabetes well controlled (Figure 4). April 2011 new episode of melena for bleeding duodenal ulcer endoscopically treated successfully with blood transfusions. Semi-annual check-ups: laboratory test values within normal limits. Negative markers. CT scan with contrast negative for recurrent disease or other condition. Last CT 2016 (Figure 5) negative for recurrent disease or other abdominal and thoracic diseases 15 years after the first surgery and 6 after the second, with the patient in good general condition.

Discussion

Given the exceptional nature of the case, especially in relation to the long interval between the first and the second manifestation of the neoplastic disease and another disease-free survival which amounts to a total duration of 15 years, it was decided to re-read the CTs and histological preparations. The first CT of 2001, which resulted in the first intervention of the pancreaticoduodenectomy on an anicteric patient, shows "a large lesion of the pancreatic head (11 cm x 5 cm x 7 cm) with large areas of necrosis of material of lesser consistency, with multiple divisions", so something that could also be described as multicystic "with distal dilation of the Wirsung duct", that is a neoplasm blocking or originating in the main duct, in short, a IPMN-MD which was an absolute indication for surgery, which proved easier due to the lack of infiltration of surrounding tissues and organs.

In the CTs performed between the first and second surgery, there was evidence of a residual pancreatic stump after the resection with irregular parenchyma with irregular margins like cystic or microcystic evolution of the organ, also in this case probably indicative of a BD-IPMN of peripheral origin.

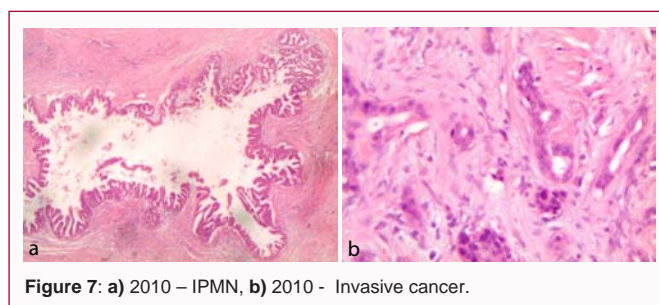


Figure 7: a) 2010 – IPMN, b) 2010 - Invasive cancer.

But it was above all clarifying the reinterpretation of old and new histological preparations ie those performed on inclusions still available from the surgical material of the two interventions. The report: (Dr. P. Visca - IRE)

Review of pathological reports of pancreaticoduodenectomy and performed in 2001: "Pancreatic tissue home to widespread intraductal papillary mucinous neoplasm (IPMN) with prevailing oncocyctic type aspects and high grade dysplasia (sec. WHO 2010) associated with invasive cancer foci (G 1-2). All examined peripancreatic lymph nodes are free of neoplasia (Figure 6a and b).

Re-evaluation of pathological slides of body-tail resection of the pancreas and spleen carried out in 2010: "Pancreatic tissue remnant home to widespread outbreaks of intraductal papillary mucinous neoplasm (IPMN) with predominant oncocyctic type aspects and high-grade dysplasia (sec.WHO 2010) in the context of extended scleroatrophy with hyperplasia of neuroendocrine areas. Finding one small outbreak of invasive adenocarcinoma (G 2) of 4 mm. Spleen unharmed (Figure 7a and b).

So in this case it was not a primitive pancreatic adenocarcinoma of tubular origin (PDAC) and certainly not a gastric adenocarcinoma as assumed before the second surgery, but an intraductal papillary mucinous carcinoma of the pancreas associated with outbreaks of invasive carcinoma (inv-IPMN) in the first operation in 2001 and an identical IPMN in the second operation associated with minimal invasive cancer outbreak. These histologic changes affect the outcome of the case, justifying the long-term survival, the negativity of markers, the absence of metastatic lymph nodes and also the general excellent condition for all fifteen years of follow up.

In the epicrisis of the case the improper descripton and diagnosis of the histological examinations reported in medical records is to be examined, a noteworthy event in medical literature, because the histological definition of IPMN was highly uncertain at the time of the 1st intervention in 2001: the interpretation of pancreatic adenocarcinoma, which was present to only a limited extent, led to the IPMN, which was almost the entire mass, being ignored. This initial error probably influenced the examination of subsequent histological examinations of biopsies and surgical specimens in which the presence of the papillary mucinous tumour was almost exclusive, while adenocarcinomal aspects were minimal.

IPMN have been defined in their histogenesis, histological morphology, biological and clinical behaviour, in the International Consensus Guidelines of [8,9].

Conclusion

Intraductal Papillary Mucinous Neoplasms (IPMN) have a potential for malignancy that differs from pre-cancerous lesions in those with malignant invasive cancer. It is reported that non-

inflammatory cystic lesions of the pancreas are very common and Kimura [10]. Reports them in about half of 300 autopsies. With the increase of widespread use of imaging asymptomatic cystic tumours have been systematically discovered. These tumours are divided into three categories: MD-main duct involving the duct of Wirsung and with the greatest risk of malignancy, those that originate from peripheral ducts (BD-branch duct) and mixed types, according to international guidelines (ICG 2006). According to the subsequent guidelines (ICG 2012) the following are evidence of a high risk for cancer: the jaundice of the pancreatic head lesion, an obvious solid component, a large dilation of Wirsung >10mm. Each of these signs entails a surgical indication.

From the histological point of view these tumours can be divided into four stages: mild dysplasia, intermediate, severe and associated with invasive carcinoma. The first two forms are referred to as benign-sec [11]. For a full and correct diagnosis above and beyond MRI and CT scans you can and should practice an endo ultrasonography with fine-needle aspiration for cytologic examination and assay of markers, as well as the endoscopic removal of pancreatic juice for cytologic examination and dosages of carcino-embryonic antigen [12]. The positivity of these tests is obviously an indication for clinical intervention; according to Han, the indications for surgical resection should be limited to the forms with abdominal pain, jaundice and dilatation of the superior Wirsung to 10 mm.

The Korean study by Han [11], noted insignificant CEA values in 290 cases of IPMN, and high values of CA 19.9 with a mean of 209 U/ml in case with prevalent localisation at the head of the pancreas. The intervention, according to the offices, was the pancreaticoduodenectomy or distal pancreatectomy, but in most patients the histological examination observes mild or moderate dysplasia for which surgical resection may be considered excessive.

Survival in such cases is sometimes surprising, with definitive healing and recurrences that are successfully reoperable. For Machado the 5-year survival for non-invasive forms varies between 77% and 100%, for invasive forms between 27% and 60%, according to a meta-analysis of the literature [13]. Out of 96 cases of IPMN operated on from 2006 to 2013, reports 46 as MD, 29 as BD and 21 as mixed, 43 were subjected to DCP, 25 as PD, 6 to segmental and 4 to TP. In follow-up 14 had developed metastases. The 5-year survival was 96% in non-invasive forms and 35% in invasive. Of the 18 patients with BD who were not operated on, all survived and remained asymptomatic. The largest is the retrospective study from Marchegiani and colleagues [14] 412 IPMN collected between 1990 and 2013 including 56% BD, 21% invasive, and 5% PDAC. There was a 17% rate of relapse, with a 5-year survival of 82% and a 10-year survival of 78%. Only 9 patients required reoperation due to recurrence, all with positive outcomes, even those with invasive forms. Interestingly, the recent study by Winter [15] of 76 cases of small IPMN with small invasive carcinoma, 66% were revealed to be multifocal. There was a local recurrence in 35% of cases and distant progression in 47%, with an overall 5-year survival of 59%. The development of neoplasia in the residual pancreatic stump was studied [16] in 195 cases operated on for IPMN. The analysis of cases made it possible to identify the multifocality of the lesions, the adenoma-carcinoma sequence and the onset of a distinct pancreatic adenocarcinoma (PDAC).

Altogether there were 13 metachronous cases in the stump of which 6 had severe dysplasia and invasive ca and 7 had concomitant ductal adenocarcinoma. These recurrences occur with an incidence

of 7.8% at 5 years and 11.8% at 10 years. The case reported by us is in line with 9 of the 412 described by Marchegiani who underwent reoperation with positive outcomes for recurrence or new tumours in the pancreatic stump remaining following previous resection; in only two cases was it PDAC. Similar activity is reported by Miyasaka, with 13 IPMN recurrences on the stump out of the 195 operated on. Like Miyasaka, Winter's 76 cases described the multifocality of IPMN lesions, their transformation into invasive cancer and the development of an autonomous adenocarcinoma on the stump, but which in their case studies represent low percentages. The case described by us has many similarities with those described by Marchegiani, Winter and Miyasaka, regarding a relapsed Inv-IPMN that underwent reoperation with resection and a positive outcome. However, it has some distinctive features. The first particularity is that probably the cephalic lesion removed in the first surgery with the pancreaticoduodenectomy was an IPMN-MD and the second intervention of a body-tail pancreatectomy was an IPMN-BD, thus confirming the multifocality of cystic lesions. The second particularity lies in the confirmation in both surgical pieces, of foci of adenocarcinoma, albeit of T1 size and therefore not yet widespread, which would confirm the evolution of the IPMN into invasive carcinoma. The third particularity stems from the fact that the presence of invasive cancer on the cystic papillary mucinous tumour was originally interpreted as a simple PADC: this could be a not uncommon event in large medical records, especially older ones, and therefore the long survivals reported for pancreatic tumours and some surprising long-term survival percentages may be related to incomplete histological diagnosis.

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