

## CASE REPORT

# Invasive Tubulopapillary Carcinoma of the Head of the Pancreas Complicated with Profuse Gastrointestinal Bleeding and Jaundice on the Background of an Intraductal Tubulopapillary Neoplasm (ITPN) of the Whole Gland

Vyacheslav Egorov<sup>1</sup>, Irene Esposito<sup>2</sup>, Natalya Ratnikova<sup>1</sup>, Natalia Starostina<sup>1</sup>, Roman Petrov<sup>1</sup>

<sup>1</sup>Moscow City Hospital No. 5, Moscow, Russia,

<sup>2</sup>Institute of Pathology, Medical University of Innsbruck, Austria

### ABSTRACT

A thirty six-year old woman was treated for acute massive upper gastrointestinal bleeding in a local hospital. A day after the bleeding she was referred to the 5th City Hospital of Moscow. Due to severe anemia and jaundice the patient was admitted to the intensive care unit and after computed tomography and endoscopy a multi-nodular tumor of the pancreatic head, body and tail with invasion of the duodenum was identified as a source of bleeding. Total duodenopancreatectomy with lymphadenectomy and splenectomy was performed few days after admission. Postoperative course was uneventful. Pathomorphological examination revealed an invasive tubulo-papillary carcinoma of the pancreatic head on the background of an intraductal tubulo-papillary neoplasm, which involved the whole pancreas. This case is the first description of intraductal tubulo-papillary neoplasm with total pancreas involvement associated with jaundice and massive gastrointestinal bleeding. This option of intraductal tubulo-papillary neoplasm natural history has to be taken into consideration in diagnostics and treatment of pancreatic tumors.

### INTRODUCTION

Intraductal tubulo-papillary neoplasm (ITPN) is a rare tumor occurring in the pancreatobiliary system, which represents less than 1% of pancreatic exocrine and less than 3% of pancreatic intraductal neoplasms [1]. ITPN was included in WHO classification of 2010 in the group of intraductal pancreatic tumors [2]. Macroscopically, ITPN looks as solid mass with necrotic areas, usually obstructing the pancreatic duct without mucus secretion. Microscopically, it is characterized by closely packed tubulopapillary structures with necrotic fields. The tumor cells are of cuboidal or prismatic with enlarged nuclei and scanty cytoplasmic mucin. The level of dysplasia is usually high, although mitotic index differs from case to case [3-9]. Clinical and histopathological descriptions of these

rare tumors are variable and still under investigation. This report is dedicated to an unusual case of ITPN with peculiar natural history and clinical course.

### CASE REPORT

A thirty six-year old woman was treated for acute massive upper GI bleeding with melena and hematemesis in a local hospital. The day after the bleeding she was referred to ICU of the 5<sup>th</sup> City Hospital of Moscow in poor condition. Physical examination revealed BMI 16.1, intensive pallor, itching, jaundice and melena. Blood and urinary tests were all within the normal ranges, except for Hb-4.7g/dl, albumin – 15 g/l, bilirubin 24 mg/dl and INR - 8.

Medical history revealed that patient without alcohol abuse or gallstone disease had been under observation for 3 years for a pancreatic head tumor. She had rejected surgery and FNA. The patient had lost 17 kg during the last year on the background of frequent diarrhea and anorexia. Jaundice appeared about 3 weeks before.

Gastroduodenoscopy revealed deformation and infiltration of the second portion of the duodenum due to an ulcerated tumor of the medial wall, covered by a large blood clot. The risk of recurrent bleeding especially under hypocoagulation was high and biopsy was denied. Abdominal ultrasonography revealed a tumor in the pancreatic head with a diameter of 4 cm, and dilatation of the bile and pancreatic duct. There was no fluid in the

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**Abbreviations** GI Gastrointestinal; ITPN Intraductal tubulo-papillary neoplasm  
**Correspondence** Vyacheslav Egorov  
Department of Surgical Oncology  
Moscow City Hospital No. 5,  
Sechenov First Moscow State Medical University  
Stromyanka str. 7, 107076, Moscow, Russia  
**Phone** + 0 79267359511  
**E-mail** egorov12333@gmail.com

abdominal cavity and no metastases were seen in the liver. Contrast multi-detector computed tomography (MDCT) showed a low density hypovascular, multi-nodular tumor of the pancreatic head and body with fuzzy configuration, maximum dimension of 11 cm and duodenal invasion. The tumor totally occupied the main pancreatic duct (MPD) from the head to the tail of the pancreas. In spite of large size, there were no signs of distant metastases and involvement of large vessels. Basing on uncommonness of radiological data, intraductal tumor growth, duodenal invasion and “cork-of-wine bottle” sign ITC on the background of ITPN was suspected (Figure 1).

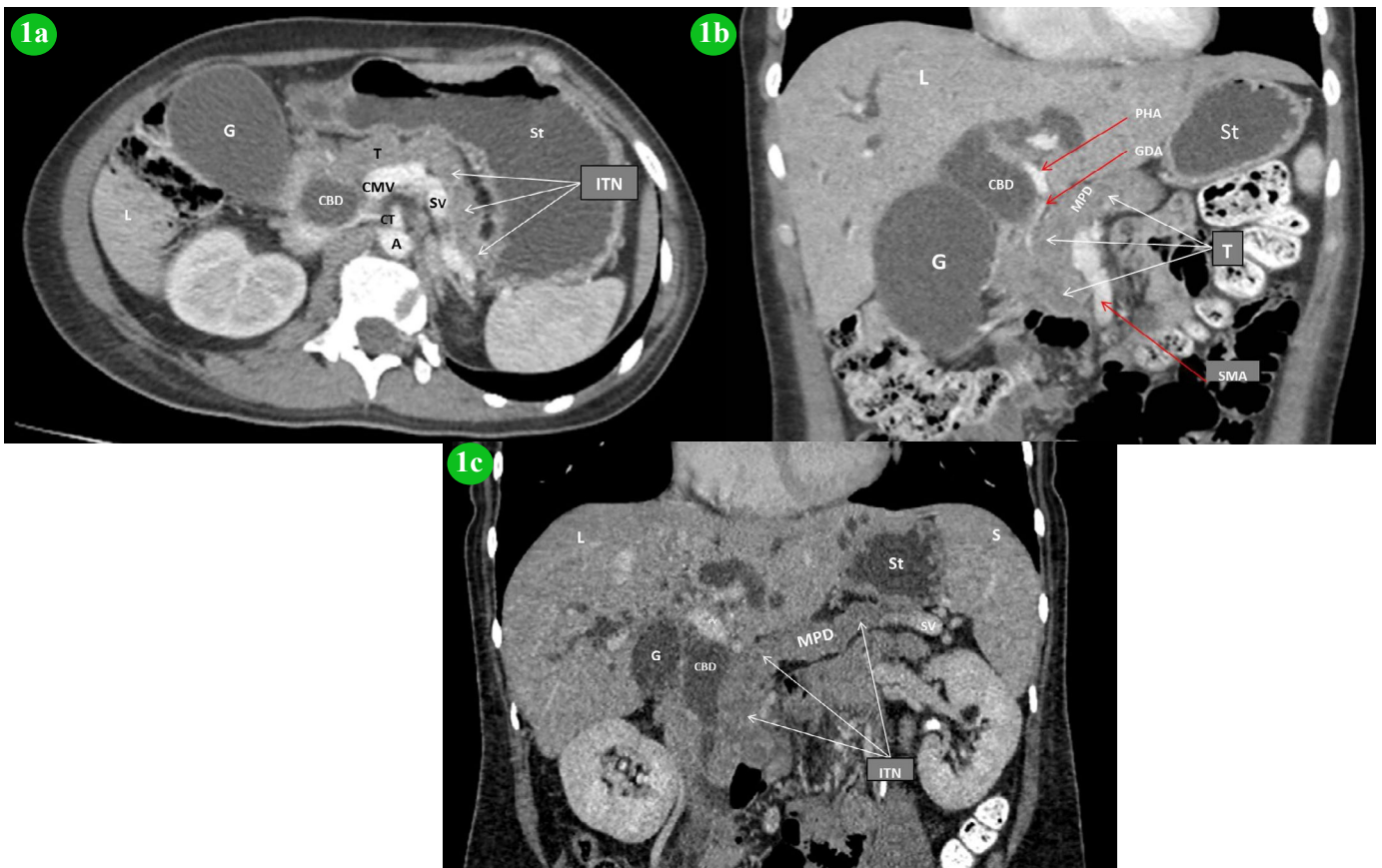
After normalization of INR, the gallbladder was drained percutaneously and 3 days later with bilirubin level of 10 mg/dl pancreaticoduodenectomy with resection of the pancreatic body was performed (Figure 2). Frozen-section biopsy showed tumor growth in the pancreatic margin and tumor structures in thick detritus, which was oozing out of the main pancreatic duct (Figure 2). It led to the completion of the procedure with total duodenopancreatectomy and splenectomy. Postoperative period was uneventful. The patient was discharged on the day 18 after insulin matching.

Macroscopic examination revealed the infiltration of most of the pancreatic head and body by a tumor with large necrotic areas, invading the duodenal wall and protruding as a polypoid mass into the duodenal lumen (Figure 2a,b). Histopathology has found closely packed tubulo-papillary structures formed by cells with high-grade dysplastic features and displaying large areas of comedo-like necroses (Figure 3). Immunohistochemical profile was the following: CK 7, 19, AE1/AE3, EMA (+++), REA, villin, CA-19-9 (+++), MUC 1(+), MUC 2, 5AC,6 (-), chromogranin (-), trypsin (-), CDX-2 (-), Ki67 head ~ 50%, Ki67 body ≤ 5%, Ki67 tail ~ 1%. Sequencing of KRAS revealed no mutations in exon 2 and 3. In 21 regional lymph nodes only reactive inflammatory changes were found. The final UICC staging was pT3N0M0. There was no microscopic residual disease (R0).

Twenty one months after surgery patient gained 9 kg, presented with no complaints, good appetite, fully restored functional abilities and currently is a housekeeper. She takes 35 units of insulin and 200 000 of pancreatin per day. Abdominal CT revealed no signs of recurrence.

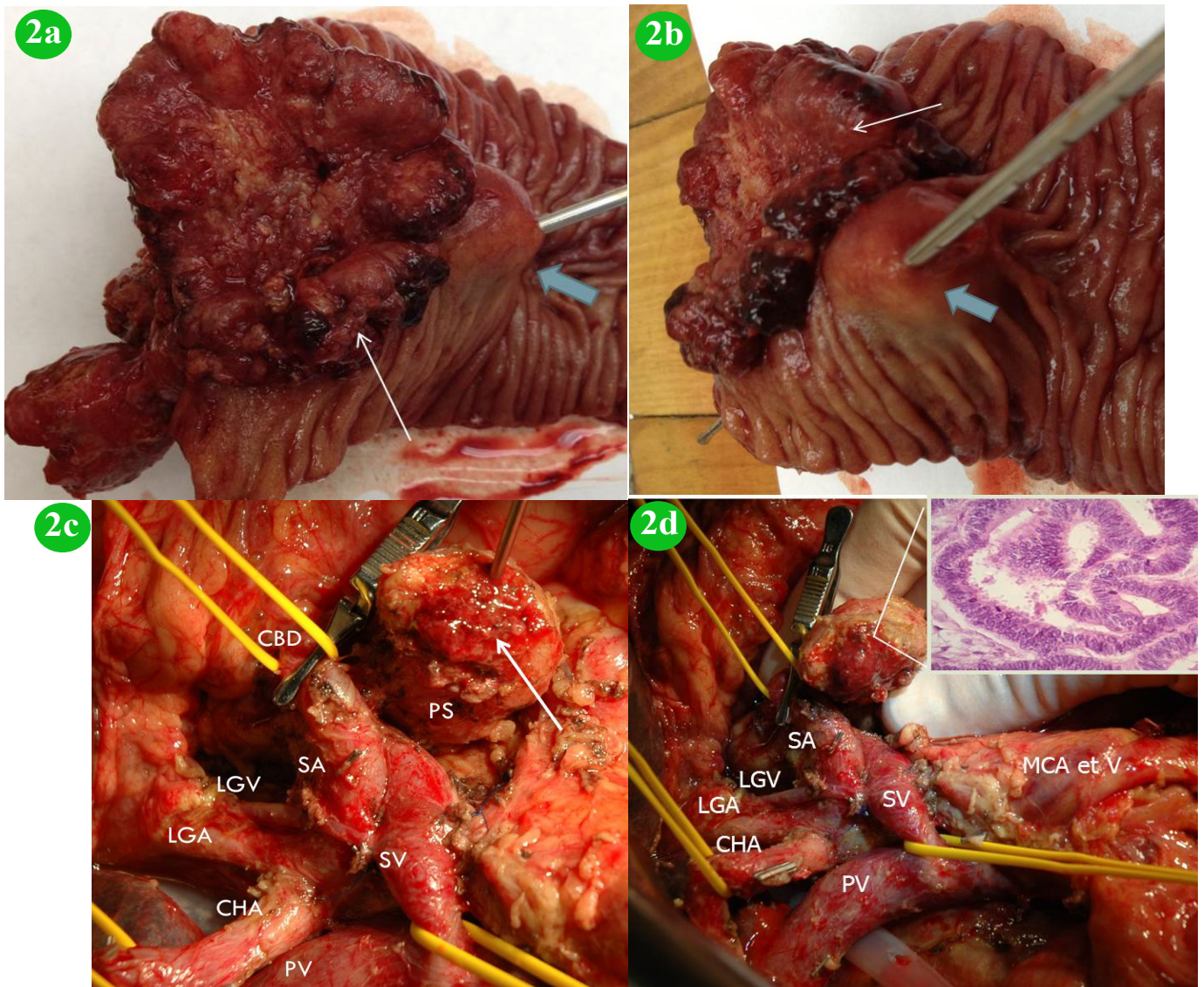
**DISCUSSION**

The term “Intraductal Tubulopapillary Neoplasm (ITPN)” was introduced by Yamaguchi and colleagues in 2009 who



**Figure 1.** MDCT the head and body the pancreas were enlarged at the expense of a tumor, which was consisted of heterogeneous nodules (without cysts and stones) up to 25 mm in diameter. (a). The size of the tumor en masse was 45x39x47 mm. The tumor density in native, arterial, venous and delayed phases was 40, 65, 72 and HU correspondingly. The spaces between nodules were enhanced in delayed phase and contained small arteries in arterial phase. (b-c). The main pancreatic duct is not well differentiated in the pancreatic head and body, filled with low density masses, irregularly dilated to 7 mm with “cork-of-wine bottle sign” at the expense of intraductal tumor growth. The body and tail are atrophic, mainly presented by the MPD. There are no signs of vascular involvement, except of one superior mesenteric vein tributary. Parapancreatic fat between the pancreatic head and duodenum is absent.

ITN intraductal tubulopapillary neoplasm; T tumor; MPD main pancreatic duct; St stomach; S spleen; L liver; G gallbladder; CBD common bile duct; A aorta; CT celiac trunk; SMA superior mesenteric artery; PHA proper hepatic artery; GDA gastroduodenal artery; SA splenic artery; PV portal vien; SMV superior mesenteric vien; SV splenic vein



**Figure 2.** Intraductal tubulopapillary carcinoma of the pancreatic head on the background of the total pancreatic ITPN. (a, b). The resected specimen after pancreaticoduodenectomy with pancreatic body removal. The carcinoma of the pancreatic head (arrow) invading the duodenum in suprapapillary area (thick arrow). (c, d) View of the operating field after pancreaticoduodenectomy with pancreatic body removal. Thick tumor detritus (arrow) is running out of the pancreatic tail duct in case of its probing (c.) or pinching (d.) the pancreatic stump (PS).

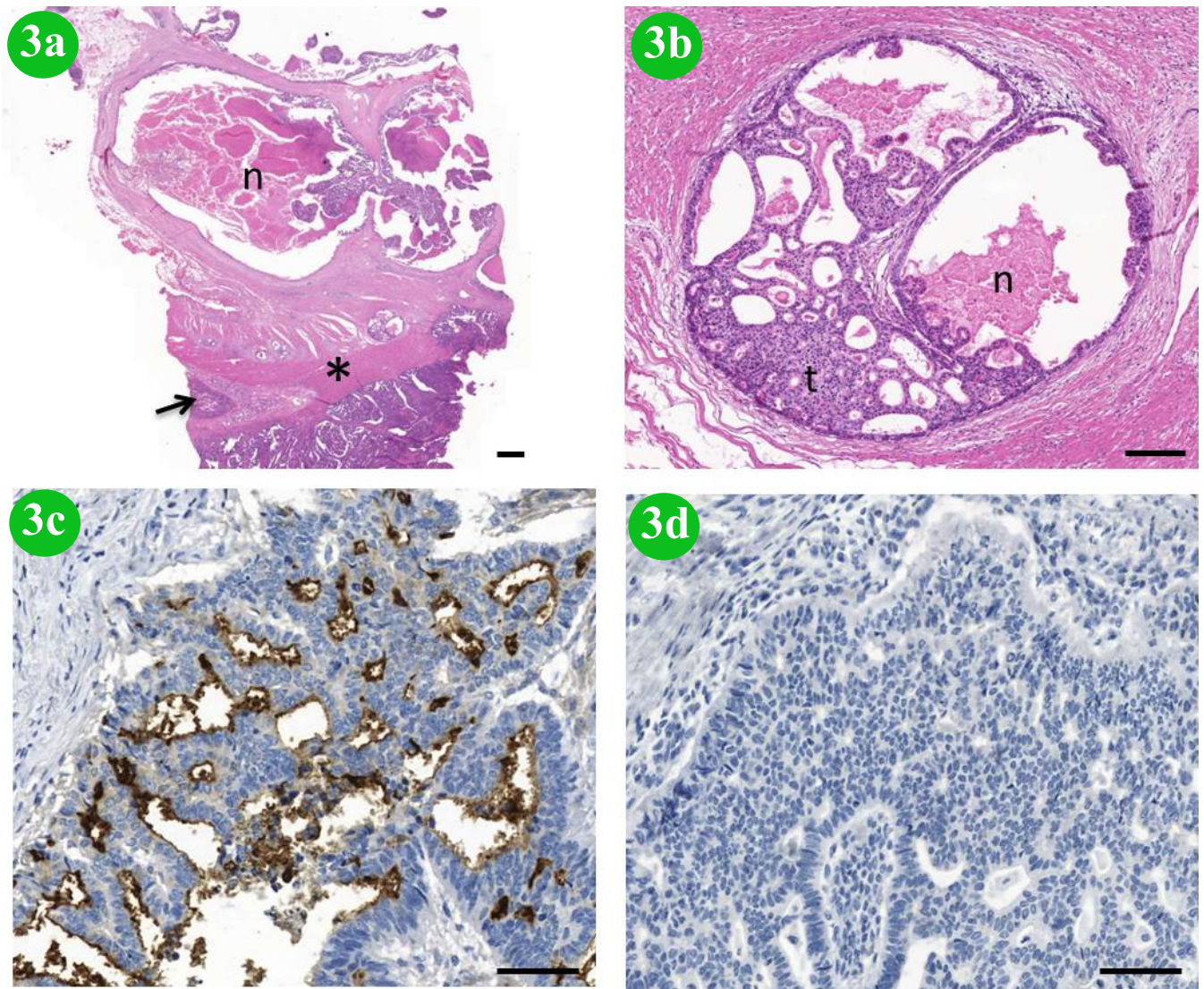
CHA common hepatic artery; CA celiac artery; LGA left gastric artery; PV portal vein; SA splenic artery (clamped); MCA medial colic artery; MCV medial colic vein; LGV left gastric vein; SV splenic vein.

had analyzed 10 cases of this rare pancreatic disease [1]. According to current WHO classification, the intraductal neoplasms of the pancreas are divided into papillary mucinous (IPMNs) and tubulopapillary neoplasms (ITPNs). The ITPNs are defined as intraductal, macroscopically visible, tubule-forming epithelial neoplasms with high-grade dysplasia and ductal differentiation without overt production of mucin [2]). The immunohistochemical profile is particularly helpful for ITPN verification as staining for MUC-1 and/or MUC-6 mucins with no expression of MUC-5 is a typical feature of this type of tumor. These different patterns of mucin staining provide basic rules for distinguishing between ITPN and IPMN [3-11]. Molecular analysis of ITPNs has not detected *KRAS* or *BRAF* mutations [6-9].

The search of journal articles published in English between 1950 and 2014 yielded 34 documented cases of ITPN (including the present one), and of those only 11 were not

carcinomas. The clinical characteristics of these tumors were as follows. Mean age of patients was around 55 years [4-17, 18-27], and the male-to-female ratio was 17/17. Tumors were localized in the head of the pancreas in 18 cases, in the body or tail in 10 cases, in the head and body in 2 cases and in the whole pancreas in 5 cases. The mean tumor size was 5.8 cm (0.8-18 cm). Tumors were asymptomatic only in five cases and were diagnosed incidentally. Abdominal pain was the most frequent symptom (16 cases), marked anemia was found in 4 and jaundice and pronounced hyperbilirubinemia – in 5 cases. All cases but one (which was diagnosed at autopsy) were treated surgically, namely, pancreaticoduodenectomy in 18 cases, distal pancreatectomy in 10 cases and total duodenopancreatectomy in 5 cases. In 5 patients with invasive carcinoma metastases were found in regional lymph nodes. Three patients died due to the progression of the disease.

Many authors have reported difficulties in not only



**Figure 3.** Upper left panel: Overview of the tumor infiltrating the duodenal wall (star). The tumor is composed by cystic (upper part of the photo) and solid areas (lower part) with large necroses (n). The arrow indicates the duodenal mucosa. Scale bar: 1 mm

Upper right panel: Detail of the tumor further showing solid and cystic components. The solid component consists of tightly packed tubules (t). Note the necrotic debris (n) in the lumen of the cystically dilated tubuli. Scale bar: 100 µm

Lower left panel: Immunohistochemistry with anti-MUC1 antibody shows luminal staining of the tumor cells. Lower right panel: No expression of MUC5AC is observed. Scale bar: 100 µm

preoperative but also postoperative diagnostics of ITPN [6, 7, 18-27]. Correct diagnosis was suspected preoperatively only in 9 cases. According to Ishigami [15], CT and MRI can visualize ITPN as a hypovascular tumor with delayed contrast enhancement and main pancreatic duct (MPD) dilation only distally to the tumor unlike the md-IPMN where the MPD is also dilated proximally to the tumor owing to increased mucin production. With a smaller tumor size, it is important to find out whether the tumor belongs to the pancreatic duct, in which case the “2-tone duct sign” and “cork-of-wine-bottle sign” can be helpful as the indicators of intraductal tumor growth on CT and MRI [23], as well as the MRCP, ERCP, endoscopic ultrasound (EUS) and transpapillary brush-biopsy methods [18-22, 26].

It was found that in ITCs decreased uptake of fluorodeoxyglucose (18F- FDG) can take place without treatment [23], which can be associated with early necrotic changes in the tumor.

The difficulties encountered with both preoperative and postoperative diagnosis demand a careful verification of each case of ITPN. When such a rare intraductal tumor is suspected, a rigorous proof must be provided to rule out other intraductal tumors of the pancreas. The immunohistochemical staining of mucins, with positivity for MUC1 and no expression of MUC5AC, enables to exclude IPMN, while negative immunostaining with antibodies against trypsin and chromogranin allows us to rule out other tumors with possible intraductal component such as the acinar cell carcinomas and neuroendocrine neoplasms [29-32]. MUC6 is often expressed in ITPN, but negative cases as the present one have been described as well [1].

The absence of *KRAS* and *BRAF* mutations is a further relevant aspect in the differential diagnosis of ITPN [3-9].

The report for the first time describes the case of a tubulo-papillary carcinoma of the head of the pancreas developing from an ITPN involving the whole pancreas and complicated

with massive gastrointestinal bleeding. Such clinical course of this rare disease must be taken into account in the diagnosis and treatment of pancreatic tumors given that the ITPN has a relatively favorable prognosis.

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## Conflict of interest

The authors declare that they have no conflicts of interest concerning this article.

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