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Reviewer A

Comment 1: Please add more representative CT or MRI images in the case 1 and case 2 according to the description of radiographic features in page 7 and 8.

Reply 1: *in consideration of the maximum number (8) of attachable figures and charts, we decided to discard most of the imaging gallery. The article aims to describe IOPNs under a histopathological point of view, therefore we favored histopathological pictures, with the hope of providing the readers further examples of typical IOPNs presentation. We hereby add the available CT scan of Case 2 in figure 1 (now divided into A and B).*

Comment 2: Please add explanation in the figure legends of Figure 1, 2, 3, 5, 6, and 7 the figures are which one, the case 1 or the case 2?

Reply 2: *as mentioned in the main text [Case 1: "Following Magnetic Resonance Cholangiopancreatography (MRCP) highlighted multiple vegetations protruding into the main and accessory ducts (figure 1)."], all available figures are related to Case 1. Given its peculiarity, we decided to select noteworthy figures exclusively from Case 1. Figure legends have been modified according to Reviewer's suggestion.*

Reviewer B

Comment 1: The issue of protecting patients' personal information. For example, as shown in Lines 8-9, page3, "A-75-years-old male patient...in October 2021.... would identify the patient information." Request that "A-70's-years-old Italian man" be stated and the "in October 2021" should be deleted.

Reply 1: *we modified sensible data regarding age and time of surgery, rounding the age and deleting the precise time of surgical intervention. CARE guidelines require a temporal landmark, therefore we decided to maintained solely the year of admission to our institution in order to minimize identification risk.*

Changes in the text:

- *A-70's-years-old Italian man presented to the general surgery department of our hospital in 2021.*
- *A-60's-years-old Italian man was referred to the general surgery department of our hospital in 2022.*

Comment 2: Abbreviation issue. For example, it is not correct that the abbreviation "CT" is suddenly used in Line 12, page3, even though there is no previous mention of it. The correct term should be "Computed tomography (CT)". Line.22, page3, "normal range" is not correct but is the "standard value (S.V.)". Line 12, page4, "IHC" should be corrected to "immunohistochemistry

(IHC)". Line 12, page4, "CK7, MUC1" should be corrected to "cytokeratin 7, mucin (MUC)1". Line 13, page4, "CD117" should be corrected to "CD117(KIT)".

Reply 2: *text changes have been made accordingly to Reviewer's suggestion.*

Changes in the text:

- *Abdominal Computed Tomography (CT) scan revealed...*
- *122 mg/dL (standard value 60-100 mg/dL), aspartate aminotransferase level of 17 IU/L (s.v. 2-31 IU/L)...*
- *on immunohistochemistry (IHC) neoplastic...*
- *positive for cytokeratin 7, mucin (MUC)1...*
- *positive for CD117(KIT) ...*

Reviewer C

Comment 1: Table 1 should include more categories, such as lymphovascular invasion, perineural invasion, lymph node status, follow up status, et al. These information will be very helpful towards further understanding of this rare entity. I would suggest to change decimal comma to point throughout. Please change "bilio-pancreatic" (Page 11, lane 13) to "pancreato-biliary" to keep consistency.

Reply 1: *recent IOPN literature – describing cases from 2019 to now – did not put emphasis on histological characteristics for each individual case. For this reason, rather than describing very fragmented data, we decided to simplify the chart. We hereby submit the table complete of all pathological categories (Authors from each study were e-mailed 4 months ago with the hope of retrieving clinico-pathological information). Text changes have been made accordingly to Reviewer's suggestion.*

Changes in the text: *common mutations in pancreato-biliary IOPNs...*

Reviewer D

MAJOR COMMENTS

Comment 1: Although the authors reported two cases of IOPN, there is no report of US/EUS or ERCP. Please mention about the results of other modalities. If the authors did not perform further examination, please mention about the reason for that.

Reply 1: *both patients did not present with jaundice nor elevation of bilirubin levels. For this reason ERCP was not performed. We added information relative to US performed in Case 1 and 2 at the moment of admission.*

Changes in the text:

- *Ultrasound (US) revealed pyeloectasia and the presence of a large mass located in the mesogastric and anterior epigastric region, requiring additional abdominal Computed Tomography (CT).*

- *US was not able to evidence the pancreatic gland due to marked meteorism.*

Comment 2: As for Case 1, why did the author perform follow up CT after one month later? Further examination should be performed during this term. Is this CT taken just before operation? Please describe the process of diagnosis that made the decision to operate for both cases.

Reply 2: the patient was scheduled for surgery and, during the waiting time, a second CT scan was performed in order to rule out the presence of vascular infiltration, that would have modified the surgical approach.

Changes in the text: *The patient was scheduled for surgery, before which a second abdominal CT showed significant enlargement of the gland with involvement of the proximal part of the main pancreatic duct (MPD). Splenic, common hepatic, gastroduodenal arteries and portal confluence were not involved by the growth. A first diagnostic hypothesis was of ITPN.*

Comment 3: On page 8, line 5. Although the author mentioned about the benefits of EUS-FNA for diagnose of IOPN, there is a possibility of tumor dissemination if EUS-FNA were performed for such a case presented here. Please discuss about this.

Reply 3: recent literature demonstrate that FNA does not significantly affect patient outcome – being peritoneal seeding an unfrequent event. Moreover, given the size and clinical presentation of both cases, Tumor Board opted for upfront surgery.

Comment 4: As for case 2, why tumor marker was not measured? How the author decided to perform surgery?

Reply 4: as reported in the text, Case 2 displayed a radiological worrisome feature, namely the absence of a clear adipose cleavage plane with the left colic flexure, giving indication to surgical intervention. Unfortunately, despite thorough consultation of the medical records, we were not able to retrieve such information.

Changes in the text: *Serum level determinations of CA19.9, CEA and CA125 were not available.*

MINOR COMMENTS

Comment 1: The author wrote all test results like 0,23 mg/dL or 8,5x8x7,5 cm. Please change 0.23 mg/dL or 8.5x8x7.5cm instead.

Reply 1: text changes have been made accordingly to Reviewer's suggestion.

Comment 2: The author wrote CA19.9. Please change CA19-9 instead. The author needs to spell out in the first place.

Reply 2: *text changes have been made accordingly to Reviewer's suggestion.*

Changes in the text: *Serum level of Carbohydrate Antigen (CA)19-9 was 23 IU/mL (s.v. 0-27 IU/mL), of Carcinoembryonic Antigen (CEA) was 1.3 ng/mL (s.v. 0-5 ng/mL) and of CA125 was 11 IU/mL (s.v. 0-27 IU/mL).*

Comment 3: What is left pancreatectomy in Page 5, line 10 ? Is this distal pancreatectomy?

Reply 3: *the term "left" has been replaced by "distal".*

Changes in the text: *The patient underwent distal pancreatectomy with splenectomy two weeks after radiological identification.*

Comment 4: Page 7, line 4 Average size of IOPNs is 5.5 cm and tend to be slightly higher than IPMNs

Higher is not appropriate. Larger is better.

Reply 4: *text changes have been made accordingly to Reviewer's suggestion.*

Changes in the text: *Average size of IOPNs is 5.5 cm and tend to be slightly larger than IPMNs [1].*