Hôpital Cantonal

Département des spécialités de médecine

Service de Gastroentérologie et d'Hépatologie

Professeur Jean-Louis Frossard

The Editorial Office of

World Journal of Gastroenterology

Dear Editor,

I would like to submit the revised manuscript n° 79388 entitled " Recent advances in the management of autoimmune pancreatitis in the era of artificial intelligence" by Sahar Mack et al. to be considered for publication as topic highlight in *the World Journal of Gastroenterology*.

We appreciated the detailed insightful comments made by the two reviewers and have made every attempt to fully address these comments in the revised manuscript. Our response are given in a point-by-point manner below extracted from the revised manuscript.

We hope the revised version is now suitable for publication and look forward to hearing from you in due course.

Sincerely yours,

Prof Jean-Louis Forssard

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Response to reviewer 1:
R: Thank you for your kind comments and guidance to enlighten the artificial intelligence section and underline this in title and abstract.

Response to reviwer 2:

1. How AIP can be differentiated from the Ductal Ca of Pancreas - add 1 para .

PANCREATIC CANCER AS A DIFFERENTIAL DIAGNOSIS

As the main important differential diagnosis of AIP is pancreatic cancer, it is important to recognize any differences in the clinical, radiological, and histological features (3,6). Clinically, AIP patients present with mild abdominal pain such as discomfort, rarely with weight loss, and fluctuant jaundice that tends to respond positively to steroid therapy. On the other hand, PDAC patients present severe, persistent, and progressive abdominal pain with weight loss and progressive jaundice. Extrapancreatic manifestations are more frequent in AIP, whereas PDAC is more localized in the pancreatic gland and induces lower bile duct stenosis, presenting metastatic lesions and direct invasion in some cases. Biologically, IgG4 is elevated in AIP patients, although elevated levels have also been reported in a few cases of PDAC (33). By contrast, elevated CA19-9 is rarely seen in AIP. Radiologically, smooth margins and capsule-like rims in the body and tail region that represent severe fibrotic changes are seen in the CT and MRI of patients with AIP. Amelioration of swelling after steroid treatment is a characteristic of AIP, whereas PDAC patients do not or rarely present an improvement. Duct dilatation should raise the suspicion of PDAC. Using contrast-enhanced CT, AIP is characterized by homogenous delayed enhancement of the gland that indicates the diffuse loss of parenchymal volume and severe fibrosis, whereas heterogenous enhancement that represents necrosis or bleeding in the tumor can be seen in PDAC. Using EUS, AIP is characterized by a duct penetrating sign as well as a diffuse homogenous hypoechoic pattern and linear or reticular hyperechoic inclusions that reflect interlobular fibrosis. In PDAC, EUS findings show a localized hypoechoic mass and a double duct sign, often accompanied by lymph node swelling or vascular invasion. Histological patterns of AIP are characterized by periductal lymphoplasmacytic infiltration, storiform fibrosis, and obstructive phlebitis. Immunohistological identification of carcinoma cells is observed in PDAC, and inflammatory reactions can be commonly observed.

2. In the imaging section - mention regarding finding in USG , CT - Scan , MRI with and without contrast in AIP.

The most typical feature is a global enlargement of the pancreatic gland associated with the loss of lobulations, giving it a sausage-like appearance (29). The capsule-like rim sign, which can also be seen with other procedures, is a relatively distinctive feature of AIP in CT. This sign is defined by a band-like structure around all or part of the pancreas. It is characterized by a lower absorption than the pancreatic parenchyma of the lesion during the pancreatic parenchymal phase and shows a delayed enhancement pattern with dynamic CT. Other elements have been described such as decreased peripheral enhancement causing a peripheral halo or ring, involution of the pancreatic tail, enhancement of the thickened bile duct wall resembling a cocoon, stenosis of the Wirsung duct

without upstream dilation, and focal hyperdense pseudotumors. MRI shows a loss of T1 signal intensity and the T2 hyperintensity of the parenchyma correlated with an inflammation of the gland. In terms of ducts, stenosis of the Wirsung duct without upstream dilation can be observed, even in the focal pseudotumors (29). A capsule-like rim reflecting the strong fibrosis of the peripancreatic lesions can be observed on T2-weighted images as a low signal and is highly specific to AIP. EUS findings in AIP can be hypoechoic with scattered high-echo spots in the enlarged area in some cases show a diffuse or localized lesion of the parenchyma and irregularities in the main pancreatic duct such as bile duct wall thickening, or produce a duct-penetrating sign (30). Further use of PET-FDG can be useful in detecting other organs involved in AIP.

3. In the AI section - details are required on how the Images were taken, processed and diagnosed. Who does the annotation of these images ?

The use of artificial intelligence in the medical domain has expanded rapidly in recent years. Artificial intelligence is a mathematical technique that automates the learning and recognition of data patterns. Diagnostic techniques such as digestive endoscopic ultrasound (DEUS) can interact with this interface. A database was developed in Rochester using DEUS images of normal pancreas (NP) and pancreas of patients with AIP, pancreatic ductal adenocarcinoma (PDAC), and chronic pancreatitis (CP) with the aim to develop a convolutional neural network, a type of network with artificial neurons that recognize and classify images (CNN) able to distinguish between these entities. For every patient in each cohort, all available still images and recorded video assets were identified and extracted. Images and videos obtained from both the radial and curvilinear echoendoscopes were included. Potentially confounding image features and patient identifying information were removed during image processing. Liver images, images with marks or annotations, and images in which calcification was visible were excluded. Using data from the training and validation subsets, various candidate CNN architectures, optimizers, and configurations were implemented, trained, and evaluated to determine an effective design for the EUS-CNN. Occlusion heatmaps were then generated and used to assess the features identified by the CNN model to differentiate all conditions (AIP, PDAC, CP, and NP). In a cohort of 585 patients (146 AIP, 292 PDAC, 72 CP, and 73 NP) with 1,174,461 extracted images, the CNN was 99% sensitive and 98% specific to differentiate AIP from NP, 95% sensitive and 71% specific to differentiate AIP from PC, 90% sensitive and 93% specific to differentiate AIP from PDAC, and 90% sensitive and 85% specific to differentiate AIP from all other pancreatic diseases (31). Other groups have used this technology to discriminate portal venous CT images with the aim to differentiate between AIP and PDAC (32).

4. Role of IV Steroid Pulse therapy, oral Methyl Prednisolone and Immunosuppressant not mentioned in the management part .

The treatment of choice – and the standard treatment at present – is corticosteroid therapy. There are currently no standard therapeutic protocols regarding the indications for corticosteroid therapy, its duration, posology, monitoring measures, and maintenance therapy. In Asia, the initial dose of prescribed oral prednisone is 0.6 mg/kg/day for 2 to 4 weeks, followed by a single maintenance dose of 7.5 mg/day for 6 months to 3 years. In the USA and Europe, the dose is 40mg/day for 4 weeks followed by a recommended reduction of 5 mg per week following symptom improvement; a single maintenance dose of 5-7.5 mg/day is recommended for 12 weeks to 6 months. A smaller dose of 30 mg/day can be given to diabetic patients (35). An alternative administration with two courses of methylprednisolone 500 mg for 3 days with a 4-day interval can be useful to induce remission in refractory cases (34).

Three treatment options exist in case of recurrence. The first approach is to maintain long-term low-dose corticosteroids (7.5 mg/day for 1-3 years), while the second is to use immunomodulator therapy such as azathioprine (2 mg/kg/day for 1-3 years) (38), methotrexate, or mycophenolate mofetil. A new therapeutic approach was proposed with rituximab, a monoclonal anti-CD20 antibody, and it seems to be a promising treatment, notably in IgG4-related disease (34,39).

5. Any triggering factors of AIP & Lifestyle modification needs to be added .

Since no triggers for AIP have been identified to date, no lifestyle modifications have been proposed.