LETTERS TO THE EDITOR

Ophthalmological follow up of patients with autoimmune pancreatitis on long-term corticotherapy

To the Editor,

I read with great interest and admiration the original paper "Ophthalmological Findings in Cases of Autoimmune Pancreatitis: Changes in Long-term Corticosteroid Therapy" by Matsubayashi et al. [1], published in the *Journal of Gastrointestinal and Liver Diseases*. This study offers rare and highly valuable ophthalmologic safety data in a systemic autoimmune condition where corticosteroids remain a principal basis of therapy. Achieving a 70-month median follow-up in a retrospective cohort is a remarkable methodological accomplishment, especially considering that patients were followed across multiple clinical care pathways.

I would like to acknowledge several strengths of this work that make it clinically relevant:

1) pathophysiologic steroid responder profiling. Recent studies confirm that steroid-induced ocular hypertension and secondary open-angle glaucoma are mechanistically linked to biologic changes at the trabecular meshwork level and increased aqueous outflow resistance via Schlemm's canal [2, 3]. Evidence shows that ocular side effects depend on more than cumulative dose alone, including peak dose at initiation and tapering dynamics over time [2-4]. Harvey et al. [2] described these mechanisms in recent publications.

2) lifestyle risk context. Smoking and alcohol intake ≥200 g/week were included as baseline co-risk factors in the corticosteroid-treated subgroup [1], both recognized contributors to oxidative stress and chronic microvascular vulnerability, which remain clinically relevant when interpreting cataract and pressure changes in steroid-exposed patients [3, 4]. Their inclusion adds credibility and clinical context to the findings [2-4].

3) autoimmune overlap awareness. The study also captured previous Behçet-related uveitis histories and tracked later inflammatory flares such as Mikulicz's disease, highlighting that ocular inflammation or intraocular pressure rise may occur during steroid withdrawal even without pancreatic relapse [1, 3-5], supporting a wider, system-level interpretation of eye risk [1, 3, 4].

4) steroid-sparing perspective. Recent literature continues to show the clinical benefit of steroid-sparing or step-down immune-modulating strategies in selected systemic autoimmune and oncologic-overlap patients [3-5].

For future work building on these observations, I respectfully suggest considering:

- starting peak dose descriptors, dose-distribution measures over time, and tapering speed when available [2-4].

- looking separately at induction-related versus withdrawal-rebound ocular inflammatory responses or IOP changes in pancreatic-stable patients [1, 3-5].

- including disease-chronicity covariates (smoking exposure length, alcohol-use history length, diabetes duration) if accessible in future cohorts [2-4].

This work offers meaningful long-term ocular monitoring data and a responsible real-world patient risk framework.

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The role of liver biopsy for the investigation of fever of unknown origin: Insights from a small cohort

To the Editor,

Fever of unknown origin (FUO) remains a significant diagnostic challenge due to its broad spectrum of potential causes. Identify the underlying etiology FUO is particularly difficult and requires a thorough, systematic evaluation. Petersdorf and Beeson defined FUO as a persistent temperature of 38.3°C (100.9°F) or higher lasting at least three weeks, with no diagnosis established after one week of inpatient investigation [1]. FUO is most commonly attributed to infections, non-infectious inflammatory diseases, and malignancies, although some cases remain unexplained. Non-infectious inflammatory disorders predominate in high-income Western countries, whereas infections are more frequent in developing regions [2]. Patients who meet FUO criteria undergo stepwise evaluation. Initial workup includes noninvasive tests such as immunological, serological, microbiological, and imaging studies, along with selected endoscopic or endocrinological assessments. Although positron emission tomography/computed tomography is increasingly used early in the diagnostic process, percutaneous liver biopsy remains an important second-line option when noninvasive investigations fail to identify the cause, alongside biopsies of lymph node, bone marrow, skin, or temporal artery.

We retrospectively reviewed 14 patients who underwent liver biopsies for the evaluation of FUO from 2000 to 2022 The mean age was 51±13 years, with the majority being women (12 patients, 86%). All patients underwent detailed imaging, including thoracoabdominal CT and abdominal ultrasonography. Viral serologies [hepatitis B, hepatitis C, Ebstein-Barr virus (EBV), cytomegalovirus (CMV), and human immunodeficiency (HIV)] and other relevant laboratory tests were performed in all cases. Liver biopsy was performed because of persistent fever accompanied by unexplained liver enzyme abnormalities (either transaminase elevation or cholestasis) despite extensive noninvasive evaluation. All patients were negative for HIV and other viral serologies. Pathological evaluation of the liver biopsies revealed nonspecific findings in 71% of cases (10 patients). Specific diagnoses were made in four patients: two with EBV hepatitis, one with tuberculosis, and one with a lymphoproliferative disorder. In the final assessments of the 10 patients with nonspecific biopsy findings, diagnoses included Still's disease (3 patients), lymphoproliferative disorders (3 patients), small vessel vasculitis (1 patient), and visceral leishmaniasis (1 patient), while 2 patients remained undiagnosed. The lymphoproliferative cases were diffuse large B-cell lymphoma. In one patient, imaging demonstrated predominant hepatic involvement without accessible lymphadenopathy, and the diagnosis was established directly from the liver biopsy. In the remaining three patients, liver biopsy findings were non-specific, and the diagnosis was made through subsequent hematological investigations. Among the 5 patients with a pre-diagnosis of tuberculosis, only one had granuloma consistent with tuberculosis (Fig. 1), confirming the diagnosis histopathologically. In one patient diagnosed with EBV hepatitis based on positive EBER staining (Fig. 2), follow-up evaluation revealed an increase in EBV viral load.

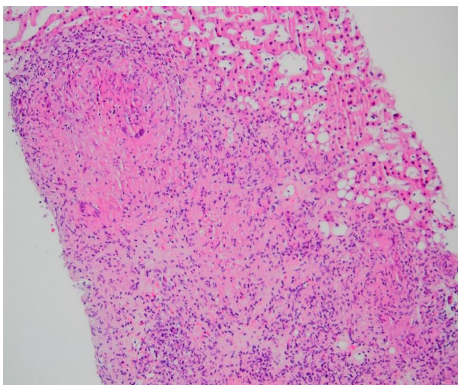

Fig. 1. Hematoxylin–eosin staining (x10) shows granulomas with a tendency to coalesce, characterized by central coagulative necrosis.

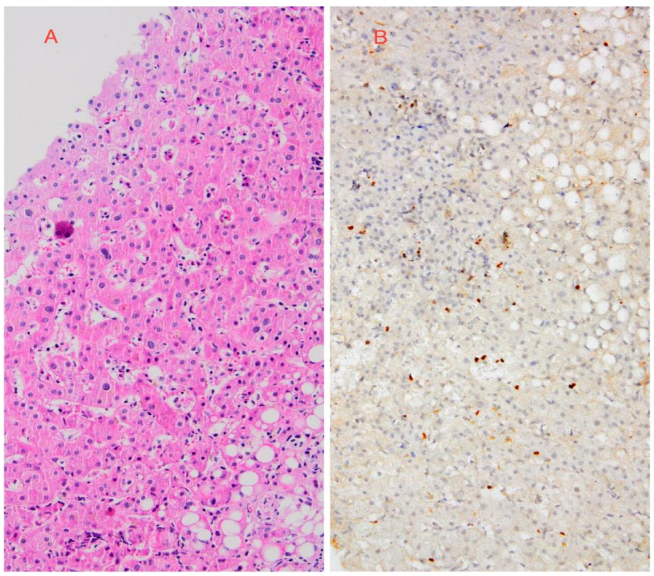

Fig. 2. A) Hematoxylin–eosin staining (x10) shows moderate lymphocytic inflammation in most portal tracts, focal interface necrosis, and multiple necroinflammatory foci within the parenchyma, consistent with hepatitis-type injury. (B) EBER in situ hybridization (x10) demonstrates scattered positivity in lymphocytes within the parenchyma, sinusoids, and portal tracts.

Holtz et al. [3] retrospectively evaluated 24 patients who underwent liver biopsy for FUO, finding that only 16.7% of patients had diagnostic liver pathology (3 with histoplasmosis and 1 with tuberculosis). On the other hand, the percutaneous liver biopsy was diagnostic in 50.5% of 107 acquired immune deficiency syndrome (AIDS) patients with FUO, where the primary pathology was *Mycobacterium avium* or *M. tuberculosis*

infection [4]. In our cohort, the liver biopsy was diagnostic only in 29% of 14 patients. In a recent systematic review on FUO in people living with HIV, tuberculosis emerged as the leading cause, with nontuberculous mycobacterial infections, leishmaniasis and pneumocystis pneumonia reported less frequently [5].

Although liver biopsy is one of the second line standard tests for patients with FUO, the literature about benefit of it is extremely limited.

Our study and two others suggest that the diagnostic yield of liver biopsy in immunocompetent FUO patients is between 16% and 29%. This contrasts with its higher utility in patients with AIDS, where it can help diagnose tuberculosis in up to half of the cases. Therefore, the decision to perform a liver biopsy must be patient-centered, considering endemic diseases, the patient's immune status, and the benefit-risk balance.

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Sclerosing cholangitis associated with dabrafenib–trametinib therapy: BRAF/MEK inhibitors should be considered

To the Editor,

Drug-induced secondary sclerosing cholangitis (SSC) represents a specific form of drug-induced liver injury. It is typically characterized by obstructive cholestasis and jaundice. The most commonly implicated drug class is immune checkpoint inhibitors [1]. Targeted therapies directed at the MAPK pathway, particularly the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib, have become essential treatment options for BRAF-mutated malignancies. Despite their clinical efficacy, the hepatobiliary toxicity profile of these agents remains incompletely understood [2]. Here, we describe what appears to be a previously unreported case of drug-induced SSC associated with dabrafenib–trametinib combination therapy.

An 81-year-old male with BRAF-positive metastatic lung adenocarcinoma had been receiving combined dabrafenib and trametinib therapy for 25 months. His medical history included only diabetes mellitus and hypertension, managed with amlodipine and empagliflozin. He had no chronic liver disease, no history of alcohol use or herbal supplementation, and no gastrointestinal symptoms suggestive of inflammatory bowel disease. A colonoscopy performed two years earlier had shown only hyperplastic polyps.

The patient developed progressive cholestatic liver enzyme elevation during treatment. Magnetic resonance cholangiopancreatography revealed multifocal intrahepatic and hilar biliary strictures without extrahepatic obstruction. Viral serologies, autoimmune markers, and serum IgG4 levels were unremarkable. Endoscopic retrograde cholangiopancreatography demonstrated a normal extrahepatic bile duct but irregular strictures involving the hilar confluence and the right and left main hepatic ducts (Fig. 1). Endoscopic dilation did not improve the cholestasis, and a percutaneous external biliary drainage catheter was placed.

Histopathological examination of bile duct biopsies showed bile duct injury with periductal fibrosis and plasma cell infiltration, consistent with drug-induced sclerosing cholangitis. No IgG4-positive plasma cells and malignancy were identified. Following cessation of dabrafenib–trametinib therapy and initiation of corticosteroids, the patient exhibited gradual biochemical improvement. He has now been followed for approximately one year without biliary stenting. Corticosteroids were discontinued, and he remains clinically well with normal bilirubin levels and mildly elevated alkaline phosphatase (approximately 1.5× upper limit of normal).

To our knowledge, sclerosing cholangitis has not previously been documented as an adverse effect of either dabrafenib, trametinib, or their combination [3, 4]. Although causality cannot be established with absolute certainty, the temporal relationship with therapy, exclusion of alternative etiologies, characteristic histopathological findings, and clinical and biochemical improvement following drug withdrawal strongly support a drug-induced mechanism.

This case suggests that MAPK pathway inhibition may rarely induce an immune-mediated or idiosyncratic cholangiopathy, expanding the spectrum of hepatobiliary toxicities associated with these agents. Awareness of this potential adverse event is crucial, as early recognition and discontinuation of therapy may prevent disease progression. We believe this observation warrants consideration in future pharmacovigilance efforts and may stimulate further research into the mechanisms underlying targeted therapy–related cholangiopathies.

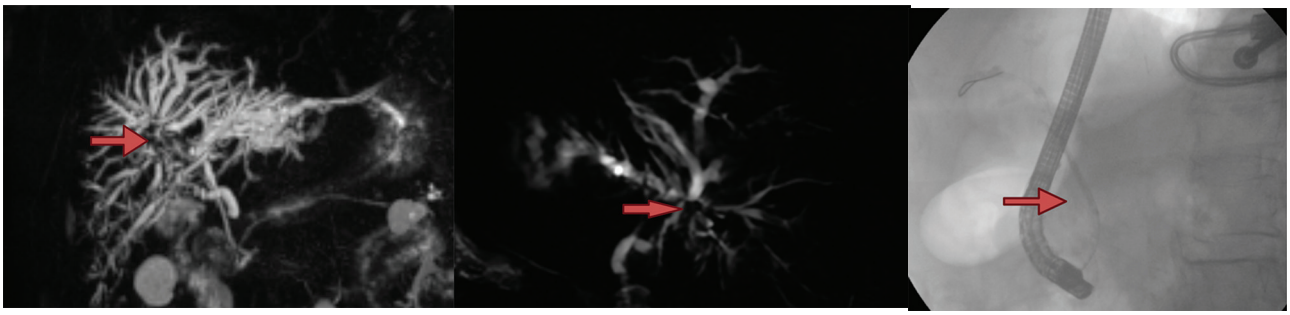

Fig. 1. A and B Magnetic resonance colangiography; C) endoscopic retrograde colangiography. The red arrows show the stenotic hilus, normal common bile duct and irregularly dilated intrahepatic bile ducts.

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Solitary plasmacytoma presenting with dysphagia

To the Editor,

A 62-year-old woman, complaining of worsening dysphagia for both solid and liquid foods for about six months, was referred from another hospital for further evaluation. She had undergone upper endoscopy at that hospital about a month before. An esophageal bulging mass of about two centimeters diameter with some superficial erosion was found. Histology of the lesion was unremarkable, and she was sent to our unit for in-depth assessment. A repeated upper endoscopy confirmed the above findings. An endoscopic ultrasonographic study revealed the presence of a sub-epithelial oval lesion of 18 x 12 mm with homogeneous echo-pattern and net margins, apparently originating from the fourth (muscular) layer (Fig. 1, left panel). An echo-guided biopsy was performed. Histological assessment revealed the presence of an anaplastic plasmacytoma (Fig. 2, right panel). The patient was sent back to the referring physicians and was then evaluated by their hematologists for the therapeutic approach. However, the disease proved to be unresponsive to several different chemotherapies, with a rapid dissemination that led to the death of the patient in a few months.

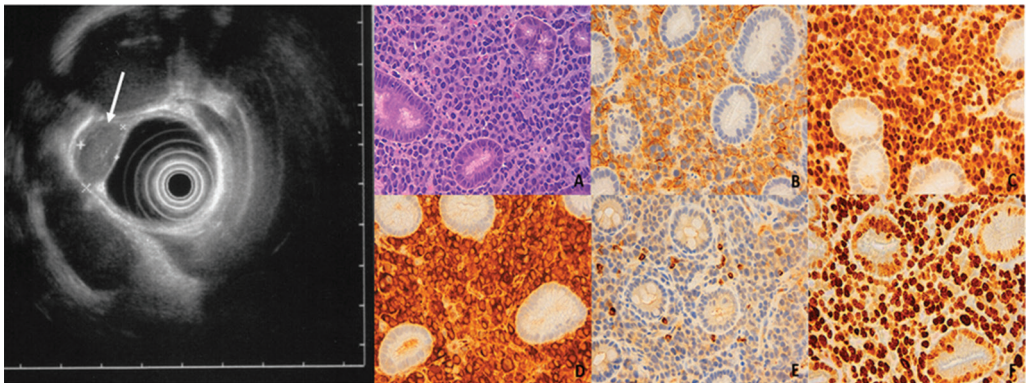

Fig. 1. Left panel: esophageal ultrasound image showing the sub-epitelial lesion (arrow). Right panel: H&E highlights neoplastic plasma cells, with plasmoblastic morphological features (A, 400X), showing diffuse positivity for CD138 (B, 400X), MUM1 (C, 400X). Clonally expression of Kappa light-chain immunoglobulin is depicted (D, 400X); in contrast, few scattered Lambda light-chain positive plasma cells are depicted (E, 400x). The neoplastic population has a very high proliferative rate (F, Ki-67, 400x)

Plasmacytoma is a plasma cell neoplasia similar to multiple myeloma, and it is divided in three categories according to the International Myeloma Working Group: 1) solitary plasmacytoma of bone, extramedullary plasmacytoma, and multiple plasmacytomas (primary or recurrent) [1]. Solitary extramedullary plasmacytomas of the gastrointestinal tract are rare entities and account for about 5% of these forms, most of which are localized in the small bowel [2, 3]. First described in 1976 [4] the esophageal involvement is even rarer, and to date reported less than ten times as single case descriptions [5]. The clinical presentation is usually heralded by worsening dysphagic symptoms, and upper endoscopy often only reveals an esophageal mass with unremarkable characteristics. Thus the histologic examination, as in our case, is of paramount importance in that reveals an unsuspected finding. However, sometimes the biopsy samples are superficial, and do not allow to characterize the mass. We want to stress that the introduction of endoscopic ultrasound may further help the diagnostic process, by allowing more in depth and precise tissue sampling. Unfortunately, the prognosis of these patients is frequently ominous. It is however important to be aware also of these rare conditions, in order to diagnose them as early as possible to try to characterize and differentiate them from other neoplastic conditions of the esophagus, that necessitate different therapeutic approaches.

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Successful treatment by hemostatic powder spray for massive gastrointestinal bleeding in an elderly male with duodenocolic fistula

To the Editor,

A 74-year-old male with pneumonia and respiratory failure developed persistent melena during the past 20 days. Because his bleeding episodes cannot be stopped by conservative treatment at his local hospital, he was transferred to our department. Gastroscopy identified multiple ulcers at the duodenal bulb and a perforation in the posterior wall of duodenal bulb. During endoscopy procedure, the patient's respiratory rate increased and his blood pressure substantially rose. Thus, this procedure had to be stopped. Because of multiple comorbidities, including a history of cerebral infarction, diabetes, and type I respiratory failure, surgery and anesthesia were declined. After 4-day blood transfusion and medical treatment, he still developed melena, and his hemoglobin concentration decreased to 52 g/L. Thus, after obtaining the informed consents from this patient's son, repeat endoscopy was performed, demonstrating an internal fistula connecting from the perforation on the posterior wall of duodenal bulb (Fig. 1A) to the ascending colon. There were extensive blood clots on the colonic side of the fistula, as well as both the ascending colon and terminal ileum. There was no active bleeding after flushing. Then, another large ulcer lesion was also observed on the descending segment of the duodenum, with a large blood clot attached to the surface (Fig. 1B), which was considered as the source of recurrent gastrointestinal bleeding. Hemostatic powder was sprayed

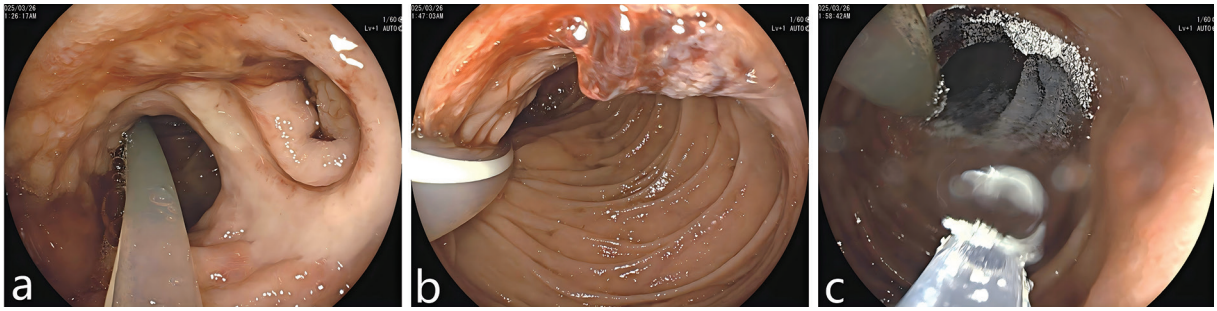

Fig. 1. Endoscopic procedures A) a duodenocolic fistula on gastroscopy; B) a large ulcer on the descending segment of the duodenum, with a large blood clot attached to its surface; C) local hemostatic powder spray.

(Fig. 1C). After that, the patient's gastrointestinal hemorrhage stopped. He resumed oral intake without any rebleeding, and his hemoglobin concentration rose to 94 g/L. The patient was discharged. Two months later, he remained in a good condition without rebleeding, and his son refused to repeat endoscopy due to its potential procedural risk.

Duodenal *perforation* is potentially life-threatening [1], especially in elderly patients [2]. Notably, this case is extraordinarily rare, since the duodenal-colonic internal fistula is simultaneously diagnosed. Due to a large ulcer with a clot, endoscopic hemostasis by local hemostatic powder spray alone was employed, which was successful without any further requirement of surgery.

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