LETTERS TO THE EDITOR

Effective endoscopic diagnosis for neoplastic or non-neoplastic reddish depressed lesions after *H. pylori* eradication

To the Editor,

We have greatly appreciated the meaningful comment of Kurtcehajic et al. [1] to our manuscript [2].

Reddish depressed lesions (RDLs) are frequently observed in the gastric mucosa after *Helicobacter pylori (H. pylori)* eradication and some cases are neoplastic lesions such as early gastric cancer (EGC). Our study investigated characteristics of both benign and neoplastic RDLs after *H. pylori* eradication especially with an attempt to depict their endoscopic features [2]. The magnifying endoscopy with narrow-band imaging (ME-NBI) demonstrated good diagnostic performance especially in the benign RDLs with 99.9% accuracy, while about 10% of the neoplastic RDLs were found to be difficult to diagnose even using the ME-NBI. We concluded that some of neoplastic RDL lesions after *H. pylori* eradication are difficult to diagnose using the ME-NBI.

Kurtcehajic et al. [1] suggested us to pay much more attention to evaluate the microvascular architecture and micro surface structure of the RDL for the precise diagnosis of lesions after *H. pylori* eradication [1]. He advised us to focus on the specific details of endoscopic microanatomy of the gastric body and antral mucosa, such as collecting venules, gastric pits (GP) and crypt openings (CO), as well as the honeycomb/coil type subepithelial capillary network (SECN) and marginal crypt epithelium (MCE). He re-analyzed our cases and demonstrated that our cases can be correctly diagnosed based on the morphologic features of the GP, CO, SECN and MCE.

We totally agree with the opinion that the more detailed characterization of endoscopic microanatomy enables us to achieve precise endoscopic diagnosis for ambiguous gastric lesions such as EGC after *H. pylori* eradication. His concept would be of great interest for the endoscopic diagnosis of EGC which might be confirmed in a future well designed clinical trial. The characterization of endoscopic microanatomy of the gastric mucosa sounds reasonable to provide superior diagnostic performance compared to simply apply the "vessel plus surface (VS) classification system" reflecting gastric pathology while deep understanding and well experience needs to achieve correct diagnosis of gastric lesion. Well established training system will be needed for the young endoscopists.

As he suggested, the ME-NBI observation is used to evaluate lesions at detailed level, while EGC after *H. pylori* eradication might also be difficult to localize using the conventional white-light endoscopy (WLE). To resolve this issue, we have recently provided evidence that Texture and Color Enhancement Imaging (TXI), a new image-enhanced endoscopy is potentially useful to enhance the EGC lesions after *H. pylori* eradication [3]. Therefore, combined use of TXI and the ME-NBI observation based on the endoscopic microanatomy would be helpful to achieve precise endoscopic diagnosis of RDLs after *H. pylori* eradication with high resolution.

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Conflicts of interest: None.
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When rapid weight loss backfires: hepatic encephalopathy from GLP-1 RA in MASH cirrhosis

To the Editor,

We would like to express our concerns regarding the potential side effects of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in patients with liver disease. For patients with metabolic-dysfunction related steatotic liver disease (MASLD) and concomitant obesity and diabetes mellitus type 2, GLP-1 RA have been proposed as potential treatment options by the European Association for the Study of the Liver (EASL) [1]. In 2016, the LEAN study first showed that patients with MASH, who were treated with liraglutide, had a higher rate of MASH resolution compared to placebo [2]. Subsequent studies confirmed these findings, demonstrating a good safety profile without major adverse events [3-6]. Until date, there is only one case report of hepatic decompensation following GLP-1 RA therapy [7]. Here, we report a case of GLP-1 RA-related side effects that led to hepatic decompensation in a patient with MASH cirrhosis.

A 55-year-old male with cirrhosis due to MASH and a model for end-stage liver disease (MELD) score of 13 presented with confusion, disorientation, and slurred speech, consistent with de novo hepatic encephalopathy (HE). Eight years earlier, he had received a salvage transjugular intrahepatic portosystemic shunt (TIPS) following severe esophageal variceal bleeding. In the intervening years, he had no further liver-related events, except for an episode of partial mesenteric vein thrombosis 12 months prior, which resolved after TIPS revision and anticoagulation. He had never experienced HE before or after TIPS. Given his obesity (BMI 35 kg/m^2), stable liver function, and the benefits of weight reduction, he was referred to endocrinology for lifestyle recommendations and GLP-1 RA therapy. In February 2024, he initiated semaglutide per manufacturer recommendations [8]. Before treatment, his Child score was B8, and MELD score was 13. Over 10 weeks, he lost 15 kg (12% of total body weight). In mid-April 2024, he reported reduced bowel movements. Days later, he presented with his first episode of HE (West Haven grade II). At that time, he was taking 1 mg semaglutide weekly. Investigations ruled out infection, hepatocellular carcinoma (HCC), TIPS dysfunction, portosystemic shunts, and portal vein thrombosis. Abdominal computed tomography showed small ascites. His admission Child score was B9, with an unchanged MELD score of 13. Other risk factors for constipation, including mechanical, endocrine-metabolic, psychological, or neurological conditions, as well as new medications, were absent. Rehydration, lactulose, and rifaximin were initiated, leading to resolution of the acute episode and discharge.

Data on GLP-1 RA in MASLD are promising, demonstrating histological improvement in MASH, positive effects on the risk of major adverse liver outcomes, as well as a reduction in death and cardiovascular events. Additionally, GLP-1 RA appear to have a favorable safety profile [5, 6]. However, our case and a previous report highlight that, in MASH cirrhosis, hepatic decompensation such as ascites and HE can occur because of weight loss during treatment with GLP-1 RA [7]. This underlines that GLP-1 RA should be administered with caution and indicates that the rather good Child scores of the patients who were initially included in GLP-1 RA studies might underestimate its potential harm [4]. We hypothesize that GLP-1 RA induced muscle loss or sarcopenia in this patient, given its established role as a major HE risk factor [1]. Additionally, since constipation is a known GLP-1 RA side effect, patients should be advised to report sudden changes in weight and bowel movements to mitigate the risk of HE.

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Posterior reversible encephalopathy syndrome due to thrombotic thrombocytopenic purpura in a liver-transplant patient treated with tacrolimus

To the Editor,

Posterior reversible encephalopathy syndrome (PRES) is a rare, acute neurotoxic condition presenting as headache, seizures, visual changes and alteration in mental status. Radiographically, it presents as vasogenic edema, most frequently seen in the parieto-occipital areas. While its cause remains unknown, it is most frequently linked to hypertension, organ transplantation, and immunosuppression using tacrolimus or cyclosporine [1].

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening thrombotic microangiopathy characterized by microangiopathic hemolytic anemia, thrombocytopenia, renal failure, neurologic impairment, and fever [2]. Posterior reversible encephalopathy syndrome and TTP are rare but severe late complications of liver transplantation (LT), and their combination is infrequent [3].

A female patient aged 48 underwent orthotopic cadaveric donor LT (OCDLT) due to hepatitis B virus (HBV)/hepatitis D virus (HDV) cirrhosis. Postoperative treatment included tacrolimus, mycophenolic acid, and steroids. The recovery was initially uneventfu except for hemorrhagic complication requiring surgical revision. On the 16th postoperative day, ultrasound (US)-guided liver biopsy was performed fdue to increased liver enzymes with ischemic necrosis diagnosed (Fig. 1A). On the 19th postoperative day, seizures and headaches were observed in the patient. Laboratory parameters revealed anemia, thrombocytopenia, elevated lactate dehydrogenase (LDH), and refractory hyperbilirubinemia. On the 20th postoperative day, bilateral cortical blindness was observed. Ultrasound imaging showed new regions of liver ischemia (Fig. 1B) and symmetrical occipital-parietal edema on a computed tomography (CT) scan-diagnostic of PRES (Fig. 1C). Peripheral smear of blood showed schistocytes, polychromasia, and nucleated red blood cells (Fig. 1D). TTP was diagnosed. Tacrolimus was discontinued, corticosteroids were increased, and plasmapheresis was initiated. The patient's clinical and radiological presentation improved with minimal three plasmapheresis treatments and tacrolimus to everolimus substitution. The follow-up liver biopsy in the patient showed resolving ischemic injury as well as the other lab tests were improved; and the patient is stable without neurological impairment at 75 months follow-up.

Thrombotic thrombocytopenic purpura and PRES, while individually documented post-LT complications, are not typically linked together. Tacrolimus, a calcineurin inhibitor, is to blame for the two conditions due to its endothelial cytotoxicity.

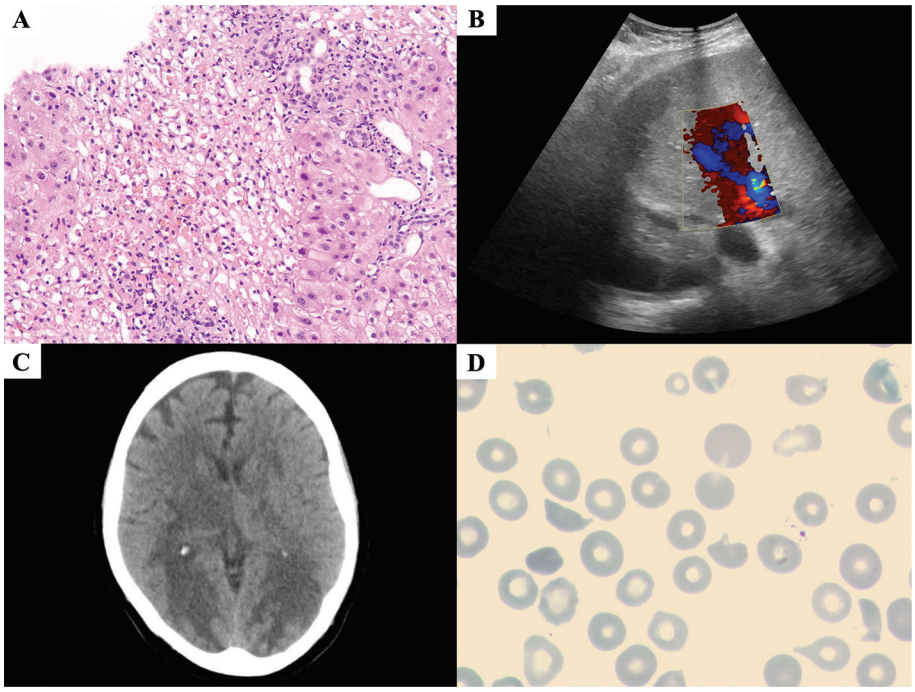

Fig. 1. Laboratory parameters during the diagnosis of thrombotic thrombocytopenic purpura (TTP) and posterior reversible encephalopathy syndrome (PRES); A) liver biopsy 16 days post-transplantation indicating large areas of coagulative necrosis and confluent lytic necrosis (H&E x200); B) liver ultrasound (US) revealed ischemic areas compatible with TTP; C) brain computed tomography (CT) showed a symmetrical vasogenic edema and confirmed PRES; D) peripheral blood microscopic examination revealed schistocytes, nucleated red blood cells, polychromasia and severe cell fragmentation pathological findings compatible TTP.

Table I. Reported cases of thrombotic thrombocytopenic purpura and posterior reversible encephalopathy syndrome following liver transplantation

Study			
Author / Year	Nwaba et al., 2013 [4]	Dashti-Khavidaki et al., 2021 [5]	Current study, 2025
Age (years) / Gender	32 / F	39 / F	48 / F
Cause of transplantation	TTP post-partum	PSC	HBV, HDV
Type of donor	N/A	Cadaveric	Cadaveric
Immunosuppressant	Tacrolimus, mycophenolate mofetil, corticosteroids	Cyclosporine, mycophenolate mofetil and corticosteroids	Tacrolimus, mycophenolate mofetil, corticosteroids
Time of presentation	1week	16 days	19 days
Symptoms	Seizures, headache, renal failure, fever	Seizures, loss of consciousness renal failure, hypertension	Seizures, bilateral cortical blindness, Renal failure
Diagnostic method	Blood tests: Microangiopathic anemia and schistocytes compatible with TTP. Renal biopsy: Vascular changes and active glomerular compatible with TTP. MRI: Changes compatible with PRES.	Blood tests: Schistocytes compatible with TTP. MRI: Intraparenchymal hemorrhage at the left occipital lobe, findings compatible with PRES.	Blood tests: Microangiopathic anemia and schistocytes compatible with TTP. CT: Symmetrical vasogenic edema within the occipital and parietal regions, compatible with PRES.
Therapy	Tacrolimus, switch to cyclosporine, plasmapheresis.	Initially reduction of cyclosporin and later, switch to sirolimus.	Tacrolimus, switch to everolimus, plasmapheresis.
Outcome	Improvement	Improvement	Improvement

F: female; LT: liver transplantation; MRI: magnetic resonance imaging; N/A: not answered; PRES: posterior reversible encephalopathy syndrome; PRES: posterior reversible encephalopathy syndrome; PSC: primary sclerosing cholangitis; HBV: hepatitis B virus; HDV: hepatitis D virus; CT: computed tomography; TTP: thrombocytopenic purpura;

Only two similar cases have been previously reported (Table I). Nwaba et al. [4] reported a 32-year-old female patient who developed PRES and TTP after LT, most likely due to tacrolimus. The patient improved considerably after drug withdrawal. Dashti-Khavidaki et al. [5] reported a 39-year-old LT recipient who had TTP and PRES complicating COVID-19 illness and cyclosporine treatment. Dose reduction of the immunosuppressant was followed by clinical improvement.

Seizures and renal impairment were the highlight in all three cases. Blood smear was the basis of diagnosis for TTP, while imaging magnetic resonance imaging or computed tomography was used for the diagnosis of PRES. Treatment consisted of withdrawal of the causative drug, plasmapheresis, and supportive management.

This case emphasizes the importance of early diagnosis and multidisciplinary treatment of PRES and TTP following LT. Because both the developments are as rare as they are, further research needs to be conducted to clarify their pathophysiologic interaction and finalize treatment protocols.

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Fibronectin hepatopathy

To the Editor,

A 44-year-old male presented to our gastroenterology clinic with fatigue and weight loss for six months. Patient had a history

of glomerulonephritis. Physical examination was notable for hepatomegaly without ascites. Laboratory tests showed hemoglobin: 9.8 g/dL, white blood cell count: 3.1x109/L, platelet count: 100x109/L, mild increased in transaminases and alkaline phosphatase, and a total/direct bilirubin: 5,07/3.89 mg/dL. Abdominal computed tomography revealed enlarged liver with a cranio-caudal length of 26 cm and decreased parenchymal density (Fig. 1a). PET-CT was within normal limits. Bone marrow biopsy showed normocellular marrow. Liver needle biopsy revealed sinusoidal deposition of amyloid-like material and mild atrophy of hepatic trabecules. Masson's trichrome stain highlighted the sinusoidal deposition in blue color (Fig. 1b). Congo red stain for amyloid was negative (Fig. 1c). Fibronectin immunostaining was positive for amyloid-like sinusoidal deposition (Fig. 1d).

Our case presented with hepatomegaly and cholestasis. Liver histology revealed the nature of the deposition with negative Congo red stain and positive fibronectin stain. Amyloid-like fibronectin deposits in the liver described as a new entity in two cases, in 2021 by Yasir et al and no other cases were reported since then [1]. Fibronectin deposition in the liver closely mimics amyloidosis with deposition of the homogenous material among the hepatic trabeculae within sinusoids. Fibronectin hepatopathy is a rare cause of hepatomegaly with shares similar histologic features of amyloidosis.

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Immune checkpoint-induced esophagitis: diagnostic challenges and clinical implications

To the Editor,

Pembrolizumab is a humanized monoclonal antibody that binds to the programmed cell death protein 1 (PD-1) receptor on T-cells, preventing its interaction with PD-L1 and PD-L2 [1]. Normally, PD-1 signaling dampens T-cell activity, but by preventing this interaction, pembrolizumab reactivates cytotoxic T-cells, enabling them to more effectively target and destroy cancer cells [2]. In this complex interplay, pembrolizumab also interferes with the key mechanisms that prevent the immune system from attacking the body itself. While lower gastrointestinal (GI) symptoms like diarrhea and colitis are most reported [2], upper GI immune related adverse effects (irAEs) are increasingly recognized with widespread immune checkpoint inhibitor use. This case highlights a rare, severe pembrolizumab-related toxicity.

A 74-year-old patient with a history of melanoma treated with pembrolizumab reported the development of dysphagia

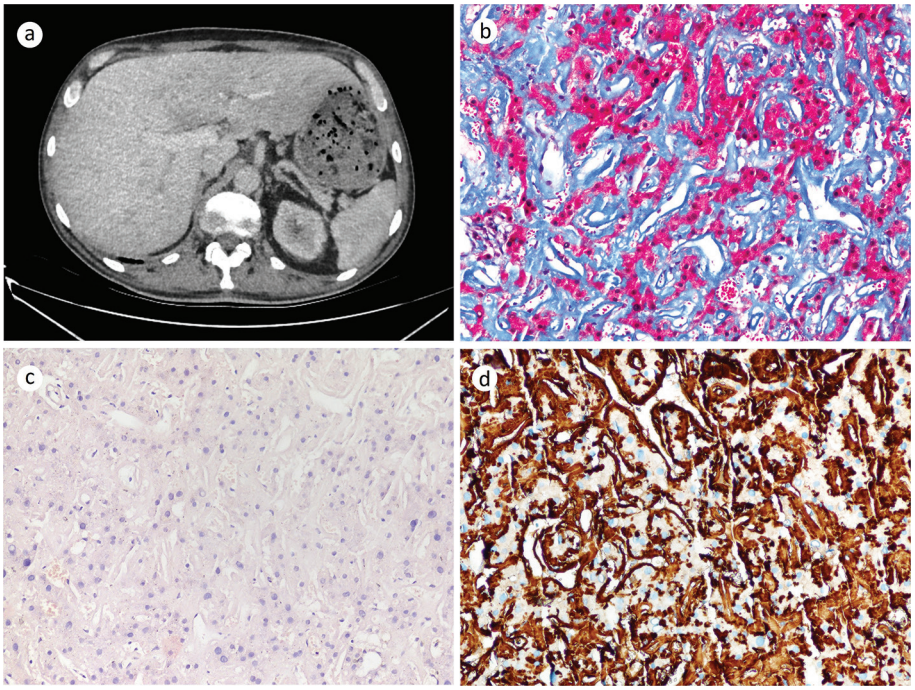

Fig. 1. (a) Abdominal CT image demonstrating enlarged liver and decreased parenchymal density. (b) Masson's Trichrome stain showing the sinusoidal deposition in blue color (x200). (c) Congo red stain for amyloid was negative (x200). (d) Fibronectin immunostain was positive for amyloid-like sinusoidal deposition (x200).

and xerostomia one month after starting pembrolizumab. She presented with xerostomia, rhinitis, and sicca-like symptoms. Autoimmune serologies were negative, and a tongue biopsy ruled out lichen planus. Conservative treatment failed, and dysphagia progressed. She was referred to gastroenterology for evaluation. An esophagogastroduodenoscopy (EGD) was performed, which appeared grossly unremarkable. Biopsies from the EGD revealed marked intraepithelial lymphocytosis, intracellular edema, dyskeratotic cells, rare intraepithelial eosinophils, and reactive atypia (Fig. 1), suggesting medication-induced esophagitis secondary to pembrolizumab. Her oncologist discontinued the medication. A one-month trial of topical steroids was initiated, and she had complete resolution of her symptoms.

Pembrolizumab's immune activation can cause irAEs. In this case, pembrolizumab's activation of T-cells likely led to intraepithelial lymphocytosis, intracellular edema, and reactive atypia observed in this patient. These findings parallel immune checkpoint-inhibitor (ICI) colitis [2]. While lower GI side effects are more commonly reported, this case adds to the growing recognition of upper GI toxicities.

Tang et al. [3] initially reported the prevalence of upper GI irAEs related to anti-PD-1/PD-L1 agents, with a median onset of six months after initiation of therapy, consistent with the timeline in this case. However, diagnosing ICI-induced esophagitis remains challenging because symptoms such as dysphagia, odynophagia, and pharyngitis overlap with other common etiologies such as reflux esophagitis and infections. This overlap delays diagnosis.

Endoscopic findings in ICI-induced esophagitis also vary widely and can range from normal (as in this case) to mild inflammation, severe ulceration, and erosion (2). Panneerselvam et al.'s [2] retrospective analysis (n=21) highlighted this variability but emphasized that histopathology consistently demonstrated both acute and chronic inflammation, akin to findings in ICI-related colitis. These findings underscore the importance of biopsies in suspected immune-mediated esophagitis, especially with unremarkable endoscopy.

Corticosteroids remain the cornerstone of treatment for ICI-induced esophagitis. In a retrospective, multicenter cohort study, patients with severe endoscopic findings, such as erosions or ulcerations, demonstrated a strong clinical response to steroids. However, follow-up endoscopy revealed that endoscopic lesions persisted in two-thirds of patients. Notably, mild cases were excluded, complicating diagnosis [4].

The largest study to-date on ICI-induced esophagitis identified key demographic and lifestyle factors associated with increased risk. Patients with ICI-induced esophagitis were more likely to be Caucasian, older than 65, and carry a history of tobacco use, alcohol use, and obesity [5]. While these factors may suggest predisposition to developing esophagitis, further research is needed to establish causality and identify predictive biomarkers to better stratify risk and guide clinical decision-making.

Pembrolizumab-induced esophagitis is a rare but clinically significant immune-related adverse event. This case highlights the diagnostic challenges of nonspecific symptoms and normal endoscopic findings, emphasizing the critical role of histopathology in confirming the diagnosis. Early recognition, multidisciplinary collaboration, and timely initiation of corticosteroid therapy are essential to preventing complications and improving outcomes. Further research is needed to better understand the epidemiology, pathophysiology, and management of this under-recognized condition.

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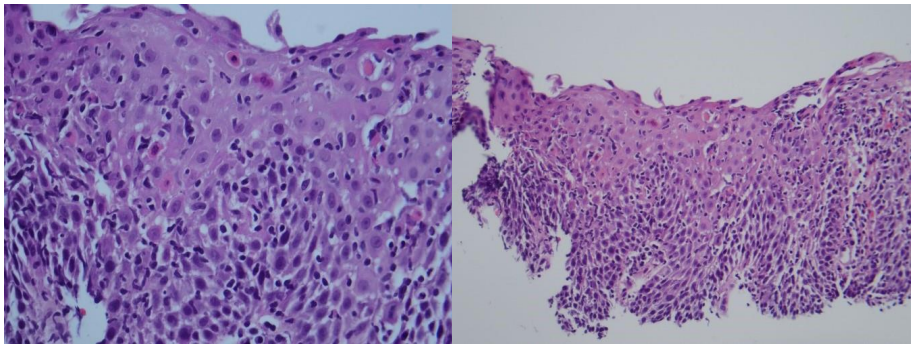

Fig. 1. Histologic findings of esophageal biopsy. (a) low-power view showing esophagitis with marked intraepithelial lymphocytosis and scattered apoptotic keratinocytes (40x). (b) high-power view highlighting intracellular edema and reactive atypia seriem (20x).

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When immunotherapy bleeds: severe hemorrhagic gastritis secondary to pembrolizumab

To the Editor,

Since its approval in 2015, pembrolizumab has revolutionized the treatment of certain cancers characterized by programmed cell death-ligand 1 expression or microsatellite instability. While its efficacy is well established, pembrolizumab is associated with a range of immune-related adverse events (irAEs) - most notably pneumonitis, colitis, and hepatitis. Gastritis, however, remains rarely reported [1].

We herein report the case of a 30-year-old female with a history of multidrug-resistant metastatic choriocarcinoma, diagnosed two years prior, who presented with sudden-onset hematemesis. She had received her seventh cycle of pembrolizumab 11 days before admission. The patient reported decreased oral intake, vomiting, worsening epigastric pain, and weight loss over the preceding month. She had been taking ibuprofen 600 mg every six hours as needed for pain.

On presentation, her vital signs were stable. Laboratory studies revealed a hemoglobin of 11 g/dL, platelet count of 262 x 10^3/µL, and INR of 1.13. Contrast-enhanced computed tomography of the abdomen and pelvis showed no significant abnormalities. Urgent esophagogastroduodenoscopy (EGD) revealed diffusely friable gastric mucosa with spontaneous bleeding throughout the stomach (Fig. 1A). No endoscopically treatable lesion was identified (Fig. 1B).

Given concern for an irAE from pembrolizumab, intravenous methylprednisolone at 1.5 mg/kg/day was initiated immediately post-procedure. Gastric biopsies demonstrated severe active chronic inflammation with cryptitis, crypt abscesses, crypt dropout, and increased crypt epithelial apoptosis - findings consistent with pembrolizumab-induced gastritis (Figs. 1C, 1D). Superficial mucosal erosions suggestive of injury from non-steroidal anti-inflammatory drugs (NSAIDs) were also noted (Fig. 1C). Pembrolizumab was discontinued, and the oncology team planned to resume chemotherapy. The patient was advised to avoid NSAIDs and was discharged on a prednisone taper and omeprazole 40 mg twice daily.

Unfortunately, she re-presented with hematemesis 10 days later. Repeat EGD and biopsy findings were consistent with prior results. She again required intravenous methylprednisolone and was discharged on a longer prednisone

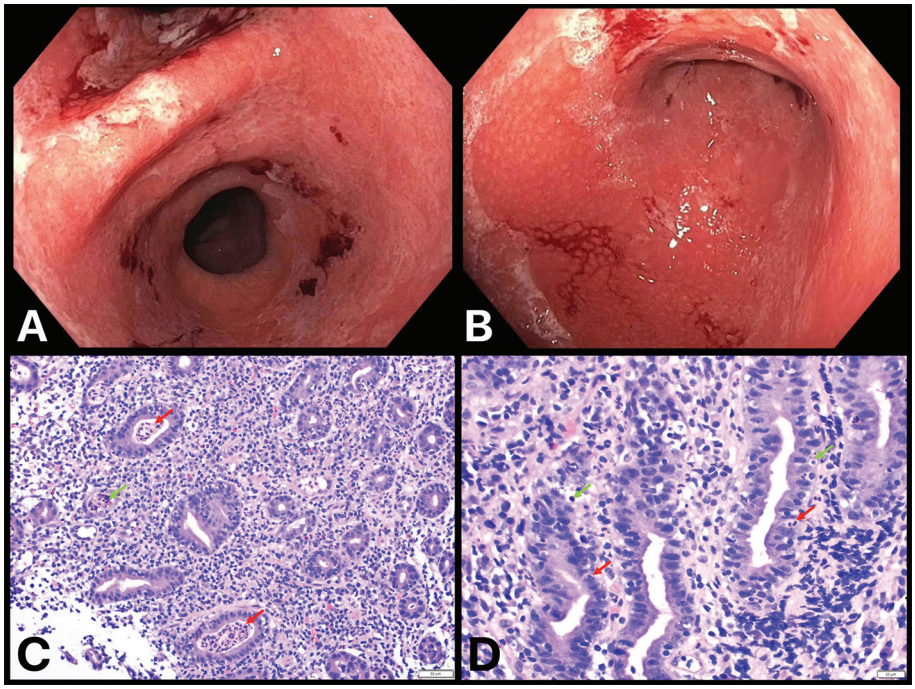

Fig. 1. (A) esophagogastroduodenoscopy showing the incisura of the stomach with diffusely friable mucosa and spontaneous bleeding, suggestive of pembrolizumab-induced gastritis. (B) diffuse mucosal friability and oozing without any endoscopically treatable lesions. (C) low-power view of gastric biopsy demonstrating severe active chronic gastritis with crypt abscesses (red arrows), crypt dropout (green arrow), and lamina propria infiltration by lymphocytes, plasma cells, and neutrophils. Eroded surface epithelium is visible in the lower right. (Hematoxylin and eosin [H&E], scale bar = 50 µm) (D) high-power view showing neutrophilic infiltration of gastric crypts (red arrows) and increased crypt epithelial apoptosis (green arrows), a hallmark of immune checkpoint inhibitor toxicity. (H&E, scale bar = 20 µm).

taper with continued proton pump inhibitor therapy. At two-month follow-up in the gastroenterology clinic, she reported complete symptom resolution.

Patients with pembrolizumab-induced gastritis typically present with dyspepsia, nausea, or vomiting, but hemorrhagic complications such as hematemesis, as seen in our case, may occur [2]. Prompt recognition of gastrointestinal (GI) symptoms and patient education regarding potential irAEs are crucial. In this case, delayed presentation likely contributed to the severity. Additionally, co-administration of GI mucosal irritants such as NSAIDs or anticoagulants should be approached with caution.

Interestingly, bleeding occurred after the seventh pembrolizumab cycle. While some retrospective studies suggest a higher irAE risk after multiple infusion numbers [3], other data do not demonstrate a consistent correlation with treatment duration [2]. Our case highlights the need for continued vigilance throughout the course of therapy. Moreover, the recurrence of hematemesis even after pembrolizumab discontinuation illustrates the variable timing of irAE onset and resolution.

Histologically, pembrolizumab-induced gastritis is marked by active chronic inflammation mediated by cytotoxic T-cells attacking gastric mucosa, resulting in mucosal injury and bleeding [4]. Our patient's biopsy confirmed this pattern (Figs. 1C, 1D). However, concurrent NSAID use may have exacerbated the clinical severity.

There is limited guidance on managing pembrolizumab-induced gastritis. Current strategies mirror those for checkpoint inhibitor-associated colitis and involve high-dose corticosteroids (1-2 mg/kg/day of prednisone or equivalent), followed by a prolonged taper over at least 4-6 weeks. Drug discontinuation is often required, depending on symptom severity. In steroid-refractory cases, biologics may be considered [5]. Further research is needed to evaluate the role of topical corticosteroids and biologics in managing this condition.

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Intramucosal colonic carcinoma arising in a sessile serrated lesion: supporting evidence for the serrated pathway

To the Editor,

The identification of intramucosal colorectal carcinoma, though uncommon, plays a key role in recognizing individuals at elevated risk for colorectal cancer, particularly those with hereditary syndromes. Establishing consistent diagnostic criteria is essential to avoid overdiagnosis and the potential for unwarranted therapeutic interventions [1].

We report the case of a 75-year-old male patient who was referred to our institution for evaluation of chronic constipation. His past medical history was unremarkable, with no known personal or family history of colorectal disease or hereditary cancer syndromes. As part of the diagnostic workup, a colonoscopy was performed, which identified a raised, sessile lesion located approximately 40 cm from the external anal margin. The lesion occupied roughly 20% of the intestinal lumen and measured 1.5 cm in diameter. Due to its morphology and partial fixation, complete endoscopic resection was not achievable at the time of the procedure, and targeted biopsies were obtained.

Subsequently, a staging thoraco-abdominal computed tomography (CT) scan was conducted, revealing no evidence of metastatic disease or regional lymphadenopathy. Histopathological analysis of the biopsy specimens confirmed the presence of an intramucosal adenocarcinoma arising within a sessile serrated lesion (SSL) (Fig. 1A–C). Immunohistochemical staining demonstrated preserved expression of DNA mismatch repair (MMR) proteins, effectively ruling out microsatellite instability typically associated with Lynch syndrome (Fig. 1D).

Given the diagnosis and incomplete resection, a surgical colectomy was performed. Histological examination of the resected specimen confirmed the presence of an infiltrating adenocarcinoma extending into the submucosa, with no lymphovascular invasion and no regional lymph node metastasis. The final pathological staging was pT1N0, consistent with early-stage colorectal carcinoma.

The postoperative course was uneventful. The patient is currently stable, without evidence of recurrence, and remains under regular surveillance in accordance with established follow-up protocols for early colorectal cancer.

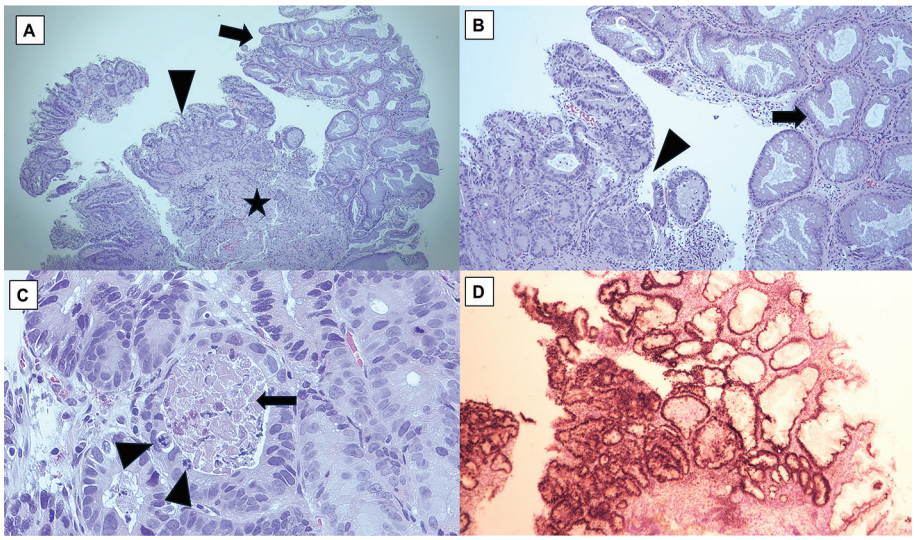

Fig. 1. An intramucosal adenocarcinoma (arrowhead) adjacent to a sessile serrated lesion (arrow). Notably, the carcinoma does not extend into the submucosa (star) (H&E, 40x) (B) at higher magnification, the area of intramucosal adenocarcinoma (arrowhead) alongside the characteristic lateral spread of the crypt bases (commonly described as boot-shaped) of the sessile serrated lesion (arrow). (H&E,100x). (C) in the area of intramucosal carcinoma, pleomorphic cells accompanied by necrosis (arrow) and several atypical mitoses (arrowhead). (H&E,400x). (D) the immunohistochemical staining for MLH1 shows preserved protein expression in both the sessile serrated lesion and the carcinoma areas (IHC,100x).

Colorectal cancer (CRC) does not arise exclusively from conventional adenomas exhibiting cytological dysplasia. A significant proportion of CRC cases originate from alternative precursor lesions, particularly serrated polyps. Advances in endoscopic imaging and resection techniques have significantly improved the detection and characterization of sessile serrated lesions (SSLs), which are typified by their subtle, flat morphology, a sawtooth appearance of the epithelial surface, and distinctive architectural features such as horizontally arranged, boot-shaped crypt bases [2]. Sessile serrated lesions are now recognized as key contributors to colorectal carcinogenesis, accounting for approximately 15–20% of sporadic CRC cases. These lesions follow a distinct molecular pathway known as the serrated neoplasia pathway [3] which is frequently associated with activating mutations in the BRAF oncogene, leading to the development of microsatellite stable or unstable CRCs depending on the status of DNA mismatch repair mechanisms.

Endoscopic techniques, including high-definition imaging, chromoendoscopy, and advanced resection methods such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), are generally effective for the diagnosis and treatment of SSLs when detected at an early stage. However, the presence of features suggestive of invasive carcinoma - such as irregular surface patterns, depressed morphology, or non-lifting signs - necessitates a more aggressive approach. In such cases, surgical resection with en bloc removal of the affected colonic segment and regional lymphadenectomy may be indicated due to the potential risk of lymph node metastasis, particularly when submucosal invasion is present [4].

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Persistent antibiotic resistance in *Helicobacter pylori* calls for revising first-line therapy protocols

To the Editor,

With the resistance rates of 27.22% to clarithromycin, 39.66% to metronidazole, and 22.48% to levofloxacin [1], the global prevalence of antibiotic resistance in *Helicobacter pylori* (*H. pylori)* demands urgent reevaluation of first-line therapy protocols in order to maintain clinical efficacy. Antibiotic

resistance is the primary reason for treatment failure in *H. pylori* eradication which is a major cause of peptic ulcers and gastric cancer. Resistance to clarithromycin and metronidazole is particularly problematic, leading to compromised effectiveness of standard triple therapy in many regions. Clarithromycin-resistant *H. pylori* has also been identified by the World Health Organization as a "high-priority" pathogen which further signifies the exigency of addressing this issue [2].

Due to the high resistance rates to clarithromycin and metronidazole observed globally, recent literature has shown the superiority of bismuth quadruple therapy (proton-pump inhibitor + bismuth + tetracycline + metronidazole) in the regions with high dual resistance [3]. For instance, Graham et al. [4] reported a 94% eradication efficacy using customized quadruple therapy, compared to 70% with traditional triple therapy. Similarly, susceptibility-guided approaches, despite requiring greater resources, exceed 90% effectiveness by aligning treatment with local resistance profiles.

Resistance rates exhibit considerable regional variation. For example, high resistance levels to clarithromycin and metronidazole in Italy and the Asia-Pacific region have influenced the choice of first-line treatments [2]. In Germany, primary clarithromycin resistance stands at around 11.3%, underscoring the need for susceptibility testing before initiating therapy [5].

Given these concerning resistance patterns, alternative therapies such as dual therapy with vonoprazan and amoxicillin, which aim to minimize antibiotic use and prevent resistance, show promising results. Genomic and proteomic analyses for the development of narrow-spectrum antibiotics, and other supportive approaches like probiotics or potassium-competitive acid blockers are also being explored, though efficacy data remain preliminary [6].

The persistent antibiotic resistance in *H. pylori* necessitates systemic changes, including the revision of first-line therapy protocols, region-specific treatment strategies, and the development of new therapeutic approaches. Critical measures such as surveillance of resistance patterns and integrating susceptibility testing into clinical practice are essential to effectively manage *H. pylori* infections and curb treatment failures. Without these systemic changes, the therapeutic landscape for *H. pylori* will continue to deteriorate.

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