

# World Journal of *Gastroenterology*

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## REVIEW

- 3535 Peroxisome proliferator-activated receptor gamma as a therapeutic target for hepatocellular carcinoma: Experimental and clinical scenarios  
*Katoch S, Sharma V, Patial V*
- 3555 Gut microbiota alteration and modulation in hepatitis B virus-related fibrosis and complications: Molecular mechanisms and therapeutic inventions  
*Li YG, Yu ZJ, Li A, Ren ZG*

## MINIREVIEWS

- 3573 Combination approaches in hepatocellular carcinoma: How systemic treatment can benefit candidates to locoregional modalities  
*da Fonseca LG, Araujo RLC*
- 3586 Update on endoscopic ultrasound-guided liver biopsy  
*Rangwani S, Ardeshtina DR, Mumtaz K, Kelly SG, Han SY, Krishna SG*
- 3595 Non-alcoholic fatty liver disease-related hepatocellular carcinoma: Is there a role for immunotherapy?  
*Mattos ÁZ, Debes JD, Vogel A, Arrese M, Revelo X, Pase THS, Manica M, Mattos AA*
- 3608 Potassium-competitive acid blockers and gastroesophageal reflux disease  
*Leowattana W, Leowattana T*
- 3620 Making the case for multidisciplinary pediatric aerodigestive programs  
*Kanotra SP, Weiner R, Rahhal R*
- 3627 Therapeutic potential of mesenchymal stem cells in the treatment of acute liver failure  
*Harrell CR, Pavlovic D, Djonov V, Volarevic V*
- 3637 Effective combinations of anti-cancer and targeted drugs for pancreatic cancer treatment  
*Nishimoto A*

## ORIGINAL ARTICLE

## Basic Study

- 3644 Mechanism of electroacupuncture and herb-partitioned moxibustion on ulcerative colitis animal model: A study based on proteomics  
*Qi Q, Zhong R, Liu YN, Zhao C, Huang Y, Lu Y, Ma Z, Zheng HD, Wu LY*

**Retrospective Study**

- 3666** How has the disease course of pediatric ulcerative colitis changed throughout the biologics era? A comparison with the IBSEN study

*Kwon Y, Kim ES, Choe YH, Kim MJ*

- 3682** Gastric mucosal precancerous lesions in *Helicobacter pylori*-infected pediatric patients in central China: A single-center, retrospective investigation

*Yu M, Ma J, Song XX, Shao QQ, Yu XC, Khan MN, Qi YB, Hu RB, Wei PR, Xiao W, Jia BL, Cheng YB, Kong LF, Chen CL, Ding SZ*

**Observational Study**

- 3695** Secular trends of intrahepatic cholangiocarcinoma in a high endemic area: A population-based study

*Lin CR, Lee YK, Chiang CJ, Yang YW, Chang HC, You SL*

- 3706** Family-based *Helicobacter pylori* infection status and transmission pattern in central China, and its clinical implications for related disease prevention

*Yu XC, Shao QQ, Ma J, Yu M, Zhang C, Lei L, Zhou Y, Chen WC, Zhang W, Fang XH, Zhu YZ, Wu G, Wang XM, Han SY, Sun PC, Ding SZ*

**SCIENTOMETRICS**

- 3720** Global research on *Clostridium difficile*-associated diarrhoea: A visualized study

*Zyoud SH*

**CASE REPORT**

- 3732** Delayed immune-related sclerosing cholangitis after discontinuation of pembrolizumab: A case report

*Tanaka T, Sakai A, Tsujimae M, Yamada Y, Kobayashi T, Masuda A, Kodama Y*

**LETTER TO THE EDITOR**

- 3739** Prednisolone induced pneumatosis coli and pneumoperitoneum

*Goh SSN, Shelat V*

- 3743** Is patient satisfaction sufficient to validate endoscopic anti-reflux treatments?

*Bortolotti M*

- 3747** Endoluminal vacuum-assisted therapy as a treatment for anastomotic leakage in colorectal surgery

*Chiarello MM, Bianchi V, Fransvea P, Brisinda G*

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## Delayed immune-related sclerosing cholangitis after discontinuation of pembrolizumab: A case report

Takeshi Tanaka, Arata Sakai, Masahiro Tsujimae, Yasutaka Yamada, Takashi Kobayashi, Atsuhiko Masuda, Yuzo Kodama

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### Abstract

#### BACKGROUND

Secondary sclerosing cholangitis, characterized by biliary obstruction, can be caused by drugs such as immune checkpoint inhibitors (ICIs). While there are a few reports of sclerosing cholangitis after immune checkpoint inhibitor administration, no case has been reported after discontinuation of such drugs.

#### CASE SUMMARY

A 68-year-old man who underwent chemotherapy for lung adenocarcinoma with bone metastasis presented with abdominal pain and fever 4 mo after the final administration of pembrolizumab. Computed tomography revealed thickening of the gallbladder wall and dilatation of the common bile duct. Endoscopic retrograde cholangiopancreatography revealed an irregularly narrowed intrahepatic bile duct. Biopsy of the bile duct demonstrated that CD8<sup>+</sup> T cells were predominant over CD4<sup>+</sup> T cells. Liver biopsy showed dominant infiltration of CD8<sup>+</sup> T in the portal tract, but onion-skin lesions were not observed. The patient was diagnosed with immune-related sclerosing cholangitis induced by pembrolizumab. Administration of methylprednisolone and endoscopic nasobiliary drainage were performed, but the cholangiography and laboratory test findings did not improve. No further treatment was administered due to disease progression, and the patient was referred for palliative care.

#### CONCLUSION

Immune-related sclerosing cholangitis may have a late onset, and such cases occurring after discontinuation of ICIs should be carefully managed.

**Key Words:** Immune-related adverse events; Sclerosing cholangitis; Delayed immune-related events; Case report

**Core Tip:** Immune checkpoint inhibitors have become a new standard in cancer treatment, but have often been reported to induce adverse events, called immune-related adverse events (irAEs). Biliary system complications, such as irAEs, remain rare, and the management strategy remains unclear. We present herein, a rare case of delayed immune-related sclerosing cholangitis (SC) after discontinuation of pembrolizumab. Our case emphasizes that immune-related SC can occur later, but the mechanisms have not yet been elucidated. As such, our case contributes to new knowledge in the hopes of being able to establish proper diagnostic criteria and management strategies for similar patients.

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## INTRODUCTION

Secondary sclerosing cholangitis (SC) is a chronic disease characterized by biliary obstruction and can be caused by a variety of specific etiologies such as infections, immune-related factors, toxicity, obstruction, ischemic injury, or drugs, including immune checkpoint inhibitors (ICIs)[1]. ICIs have transformed the treatment landscape for patients with many advanced malignancies but have often been reported to induce adverse events, called immune-related adverse events (irAEs)[2]. The irAEs differ from toxicities caused by cytotoxic or molecularly targeted agents, and the time to toxicity may be delayed and not follow a cyclical pattern, as observed with conventional cytotoxic agents[3]. Biliary system complications, such as irAEs, remain rare, and the management strategy remains unclear. There are a few reports of SC induced by ICIs; however, no cases developed immune-related SC after discontinuation of ICIs. Herein, we report a case of delayed immune-related SC caused by pembrolizumab.

## CASE PRESENTATION

### Chief complaints

A 68-year-old male patient was admitted to our hospital with abdominal pain and fever.

### Imaging examinations

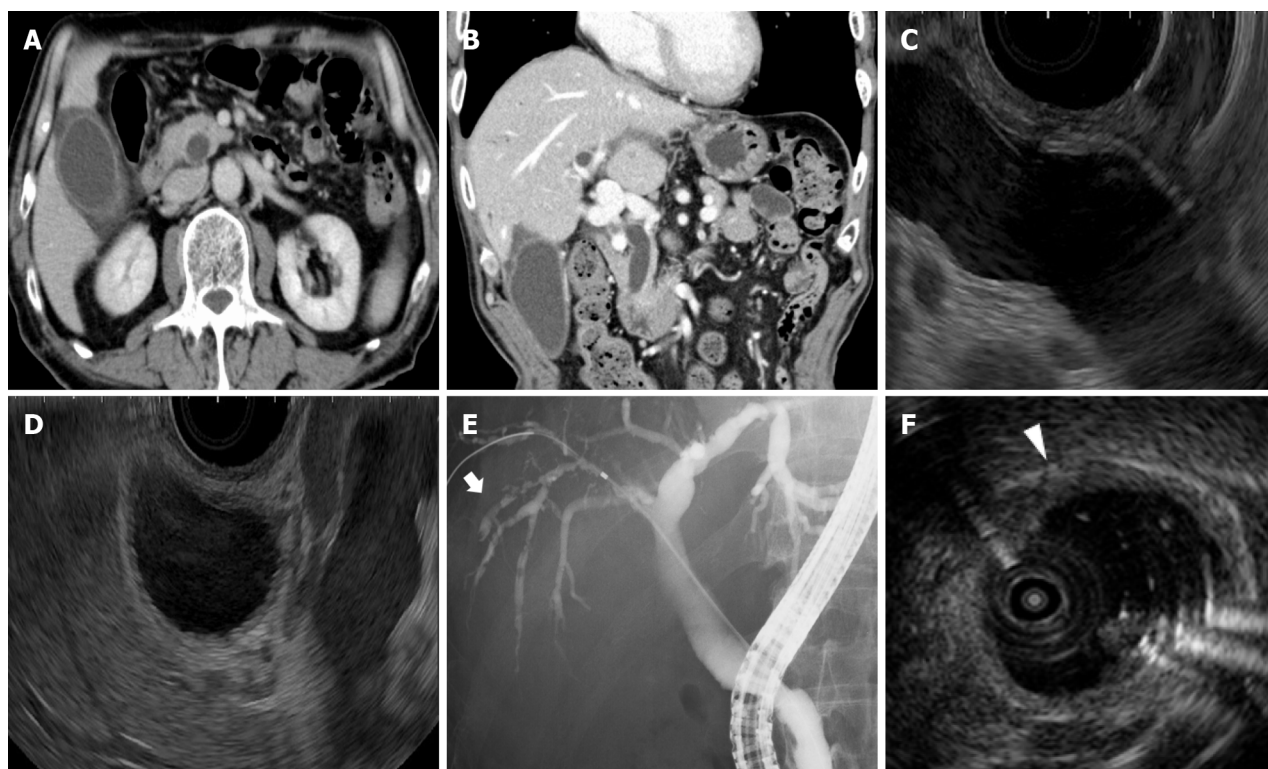
Contrast-enhanced computed tomography and endoscopic ultrasonography revealed swelling and wall thickening of the gallbladder and dilatation of the common bile duct without obstruction (Figure 1A-D). Endoscopic retrograde cholangiopancreatography revealed a dilated common bile duct and irregularly narrowed right intrahepatic bile duct (Figure 1E). Intraductal ultrasonography demonstrated diffuse wall thickening from the right bile duct to the common bile duct (Figure 1F).

### Laboratory examinations

Laboratory tests revealed increased levels of white blood cells [10100/ $\mu$ L (3300-8600/ $\mu$ L)], C-reactive protein [4.88 mg/dL (0.00-0.18 mg/dL)], aspartate transaminase [31 U/L (13-30 U/L)], alanine transaminase (ALT) [50 U/L (7-23 U/L)], gamma-glutamyl transpeptidase [205 U/L (13-64 U/L)], and alkaline phosphatase (ALP) [996 U/L (38-113 U/L)]. Total bilirubin was within the normal range [0.7 mg/dL (0.4-1.5 mg/dL)], and blood cultures showed no bacterial infection. The serum immunological markers, including antinuclear antibody, antimitochondrial antibody, and anti-smooth muscle antibody were negative, and the immunoglobulin G4 Level (59 mg/dL) was within the normal range.

### Physical examination

The patient's body temperature was 38.9 °C, but the other vital signs were stable. Regarding the pulmonary and cardiac examination, no obvious abnormality was observed. Physical examination revealed epigastric tenderness without rebound tenderness or Murphy's sign. No jaundice or palpable masses were observed.



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**Figure 1** Imaging examinations of the gallbladder and common bile duct. A, B: Contrast-enhanced computed tomography shows swelling and wall thickness of the gallbladder and common bile duct; C, D: Endoscopic ultrasonography shows dilatation of the common bile duct without obstruction and wall thickness of the gallbladder; E: Endoscopic retrograde cholangiopancreatography shows a dilated common bile duct and irregularly narrowed right intrahepatic bile duct (white arrow); F: Intraductal ultrasonography shows the wall thickness from the right bile duct to the common bile duct (white arrowhead).

### Personal and family history

No information was available regarding his family history.

### History of past illness

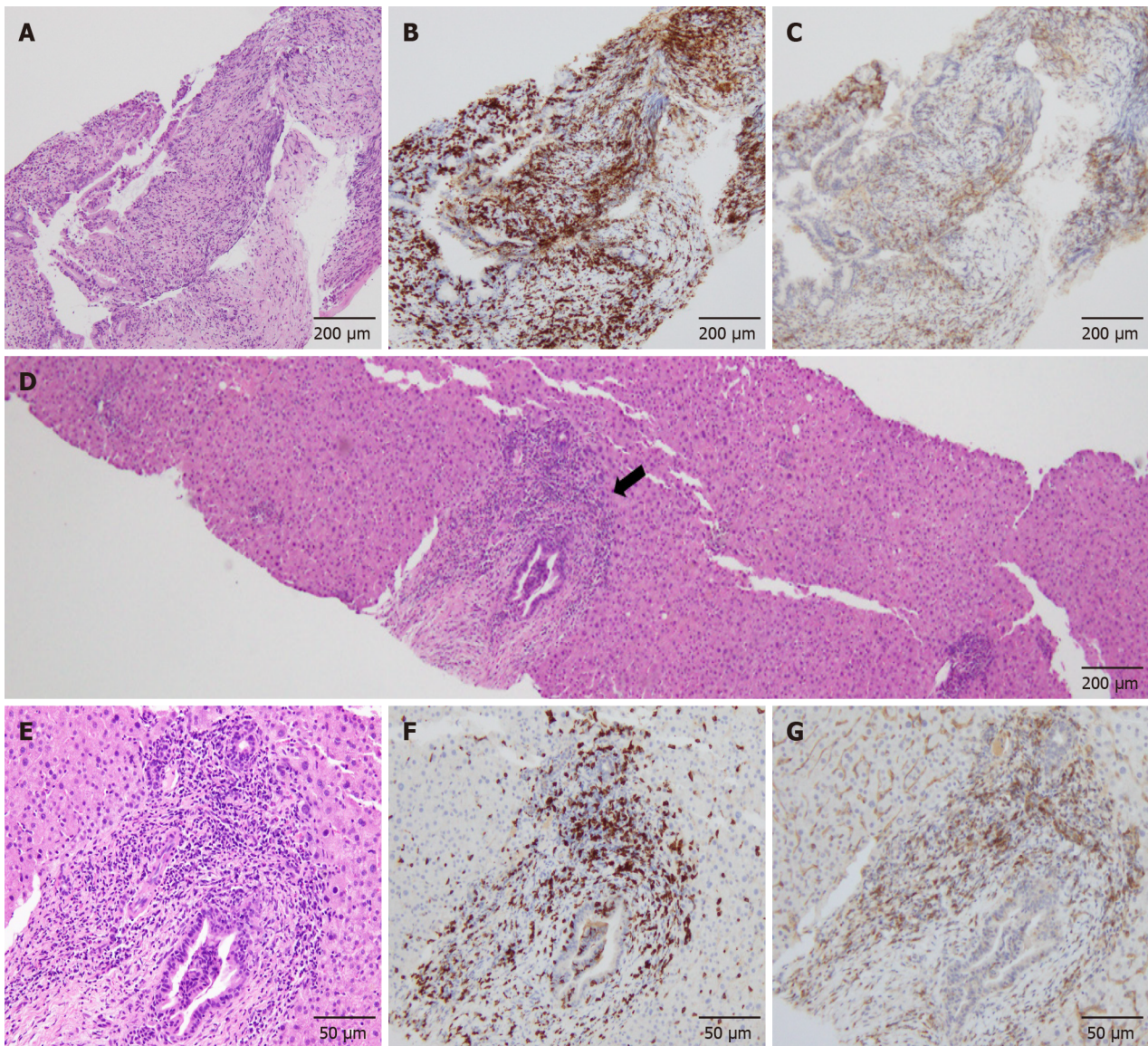
The patient has laparoscopic inguinal hernia repair twenty years ago.

### History of present illness

The patient was diagnosed with stage IV lung adenocarcinoma (wild-type epidermal growth factor receptor and anaplastic lymphoma kinase, programmed death ligand 1 positive expression) and received first-line treatment with cisplatin and pemetrexed sodium hydrate. Four months after the initiation of first-line chemotherapy, the patient received second-line treatment with pembrolizumab because of disease progression. Three months later (three cycles of pembrolizumab), carboplatin and nab-paclitaxel were administered as third-line treatments. Four months after discontinuation of pembrolizumab (3 mo after initiation of third-line chemotherapy), the patient was admitted to our hospital with abdominal pain and fever.

## FINAL DIAGNOSIS

The common bile duct biopsy showed intraepithelial infiltration of lymphocytes, and CD8<sup>+</sup> T cells were more predominant in the biliary epithelium than CD4<sup>+</sup> T cells (Figure 2A-C). Percutaneous ultrasonography-guided liver biopsy was also performed for differential diagnosis of other liver diseases. The liver biopsy showed infiltration of predominantly CD8<sup>+</sup> T cells in the portal area, but the periductal "onion-skin" fibrosis characteristic of primary sclerosing cholangiopathies, and panlobular hepatitis or isolated central zonal necrosis characteristic of acute hepatitis were not detected (Figure 2D-G). According to these imaging and pathological findings, the patient was diagnosed with immune-related SC induced by pembrolizumab.



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**Figure 2** Pathological findings of the common bile duct and liver. A: Hematoxylin–eosin staining ( $\times 40$ ): Intraepithelial infiltrations of lymphocytes are observed; B and C: CD8 (B) and CD4 (C) staining ( $\times 40$ ): Infiltration of CD8<sup>+</sup> T cells are predominant in the biliary epithelium compared to CD4<sup>+</sup> T cells; D and E: Hematoxylin–eosin staining: On liver biopsy, inflammation of the hepatic parenchyma is not observed. The periductal "onion-skin" fibrosis is not observed in the portal area (black arrow); F and G: CD8 (F) and CD4 (G) staining ( $\times 200$ ): In a zoomed-in view of the portal area, predominant infiltration of CD8<sup>+</sup> T cells, compared with CD4<sup>+</sup> T cells, is observed.

## TREATMENT

Endoscopic nasobiliary drainage was performed and administration of 25 mg (0.5 mg/kg) of methylprednisolone was initiated. However, grade 3 elevation of ALP and grade 1 elevation of ALT were still present, and the cholangiography findings did not improve.

## OUTCOME AND FOLLOW-UP

Because of disease progression, no further treatment was administered, and the patient was referred for palliative care.

## DISCUSSION

ICIs enhance antitumor immunity by blocking negative regulators of T cell function that exist on both

immune and tumor cells. Although these agents can lead to remarkable responses, their use may also be associated with irAEs. A previous study showed that most irAEs occur in the first few months of treatment, but late-onset toxicity even after ICI discontinuation is also possible[4]. To the best of our knowledge, no case of immune-related SC after pembrolizumab discontinuation has been reported.

Kawakami *et al*[5] revealed that immune-related cholangitis was characterized by: (1) Localized extrahepatic bile duct dilation without obstruction; (2) Diffuse hypertrophy of the extrahepatic bile duct wall; (3) A dominant increase in the biliary tract enzymes ALP and gamma-glutamyl transpeptidase relative to the hepatic enzymes aspartate and alanine aminotransferase; (4) Normal or reduced levels of the serum immunological markers antinuclear antibody, antimitochondrial antibody, smooth muscle antibody, and immunoglobulin G4; (5) Pathological findings of biliary tract cluster of differentiation CD8<sup>+</sup> T cell infiltration from liver biopsy; and (6) A moderate to poor response to steroid therapy. The present case met all these characteristics of immune-related cholangitis.

In contrast, SC developed while carboplatin and nab-paclitaxel were administered. Previous studies reported that chemotherapy-induced SC and drug-induced SC appeared to be one or more strictures of the large bile ducts, mainly the common hepatic duct and the right and left hepatic ducts, usually sparing the common bile duct and smaller intrahepatic ducts[6,7]. Histologically, Weber *et al*[8] showed that a shift in the CD4<sup>+</sup>/CD8<sup>+</sup> cell ratio in favor of CD8<sup>+</sup> cytotoxic T lymphocytes is useful in discriminating irAEs from other conditions (*e.g.*, autoimmune diseases and drug-induced injury). In our case, an irregularly narrowed right intrahepatic bile duct and infiltration of predominantly CD8<sup>+</sup> T cells were observed. Therefore, we diagnosed the patient with SC induced by pembrolizumab on the basis of the imaging and pathological findings of previous reports.

Recently, new reports of irAEs emerging after discontinuation of immunotherapy, a clinical diagnostic complex termed delayed immune-related events (DIRE), have surfaced[9]. The first case of DIRE after discontinuation of pembrolizumab was reported in 2013[10], and various late-onset irAEs have also been reported in the literature[11]. Anti-PD-1 antibodies continue to bind to lymphocytes several weeks after the last infusion of PD-1 inhibitors, which explains the development of irAEs after discontinuation of ICI therapy[12]. Although there have been some reports of DIRE after discontinuation of pembrolizumab, no cases of delayed immune-related SC induced by pembrolizumab have been reported.

Previous studies showed that steroid therapy was recommended for the treatment of irAEs, but was not useful for the treatment of immune-related SC[4,13]. Ursodeoxycholic acid (UDCA) and other anti-inflammatory agents, including immunomodulators and infliximab, have been considered for the treatment of irAEs, but their efficacy and response have been reported to be insufficient for the treatment of immune-related SC[14,15], and more cases may be needed to evaluate the usefulness of these drugs for immune-related SC. Biliary drainage has been reported to be ineffective for immune-related SCs[5,16,17]. It remains uncertain why there is a poor response to steroid therapy and biliary drainage for immune-related SC, and further studies are necessary to establish the treatment for immune-related SC.

This indicates that immune-related SC can occur later, similar to other hepatic irAEs. The imaging features and pathological findings of immune-related SC have become almost clear, but the mechanism and onset time of immune-related SC have not been elucidated. Further studies and accumulation of cases are necessary to establish appropriate diagnostic criteria and management strategies, and caution should be exercised for late-onset irAEs after discontinuation of ICIs.

## CONCLUSION

Immune-related sclerosing cholangitis may have a late onset, and such cases occurring after discontinuation of immune checkpoint inhibitors should be carefully managed.

## FOOTNOTES

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