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CASE REPORT

Anti programmed death-ligand 1 antibody-related cholangitis without bile duct dilation or stenosis

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Abstract
Cholangitis has been reported as an immune-related adverse event, although it rarely occurs. Here we report a case of cholangitis due to atezolizumab in a 77-year-old woman who had been treated with atezolizumab and nab-paclitaxel for breast cancer and lung metastasis. On the seventh cycle, she presented with fever and epigastric pain, and computed tomography and endoscopic ultrasound showed slight wall thickening of the common bile duct, and transpapillary bile duct biopsy was performed. Pathologically, $CD8^+$ T cells predominant infiltration was detected in the subepithelium of the bile duct, resulting in the diagnosis of atezolizumab-related cholangitis. The patient's symptoms were resolved immediately after discontinuing atezolizumab. Hepatobiliary enzymes returned to normal 21 days after onset, and bile duct wall thickening disappeared. Cholangitis should be included as the differential diagnosis of liver dysfunction in patients receiving immune checkpoint inhibitors.

Keywords Cholangitis · Atezolizumab · Immune-related adverse event · Breast cancer

Introduction

Immune checkpoint inhibitor (ICI) has been indicated for a variety of malignancies. Currently, anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody and anti-programmed cell death 1 (PD-1) antibody and anti-programmed cell death ligand 1 (PD-L1) antibody are clinically applied. While the clinical application of ICI is expanding, reports of immune-related adverse event (irAE) are also increasing. Immune checkpoint-related cholangitis is a rare irAE. In particular, only one case of anti- PD-L1 antibody-related cholangitis has been reported in English [1]. We report a case of anti-PD-L1 antibody-related cholangitis accompanied by CD8-positive T cells in a bile duct biopsy specimen without obvious bile duct stenosis or dilatation on imaging findings.

Case report

A 77-year-old female patient presented with a left breast mass. She had no medical or family history. The patient was diagnosed with breast cancer with lung metastasis (cT2N0M1 cStage IV) in June 2020. Immunostaining revealed that invasive ductal cancer cells were negative for hormone receptors and human epidermal growth factor receptor 2 and positive for anti-programmed death-ligand 1.

The patient was treated with anti-PD-L1 antibody atezolizumab (840 mg on days 1 and 15) and nab-paclitaxel (100 mg/m^2 body surface area on days 1, 8, and 15 in 28-days cycles), resulting in a partial response of the primary tumor and lung metastasis after the sixth cycle. 2 days after the start of the seventh cycle, she complained of fever (39 ℃) and epigastric pain. Blood tests showed elevated hepatobiliary enzymes, including the total bilirubin (0.3 mg/dL), aspartate aminotransferase (102 U/L), alanine aminotransferase (ALT) (137 U/L), alkaline phosphatase (ALP) (162 U/L), and γ-glutamyl transferase (123 U/L).

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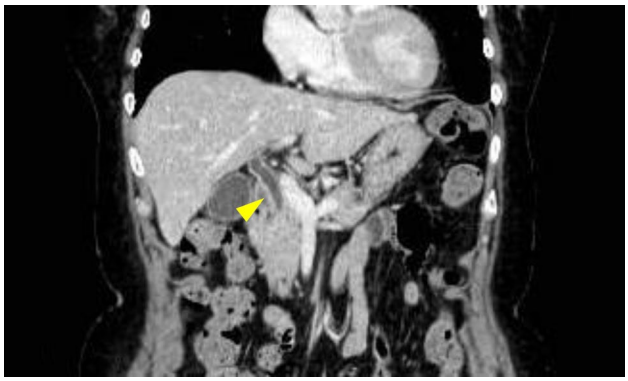

Fig. 1 Computed tomography showed a mild wall thickening in the common bile duct

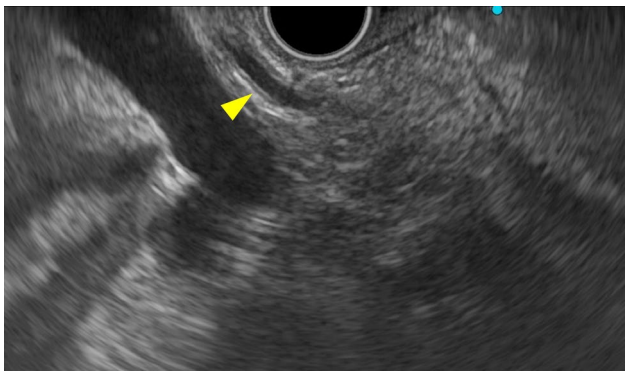

Fig. 2 Endoscopic ultrasound was performed and revealed a circumferential and homogeneous wall thickening of the common bile duct

Other parameters were normal, including IgG4 (8 mg/dL), IgG (1042 mg/dL), IgM (75 mg/dL), antinuclear antibody (< 40×), and antimitochondrial M2 antibody (1.2 U/mL). The patient was negative for hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and hepatitis C virus antibody.

Magnetic resonance cholangiopancreatography (MRCP) did not reveal any obvious bile duct stenosis or dilatation; however, computed tomography (CT) showed a mild wall thickening in the common bile duct (Fig. 1). Therefore, endoscopic ultrasound (EUS) was performed and revealed a circumferential and homogeneous wall thickening of the common bile duct (Fig. 2), which led to the suspicion of cholangitis. No bile duct stones were found. In addition, no abnormal findings were found in the pancreas.

Endoscopic retrograde cholangiography was performed. Cholangiography showed no obvious abnormal findings in the intrahepatic and extrahepatic bile ducts. (Fig. 3); however, intraductal ultrasonography (IDUS) showed a generalized wall thickening similar to EUS. The thickening was

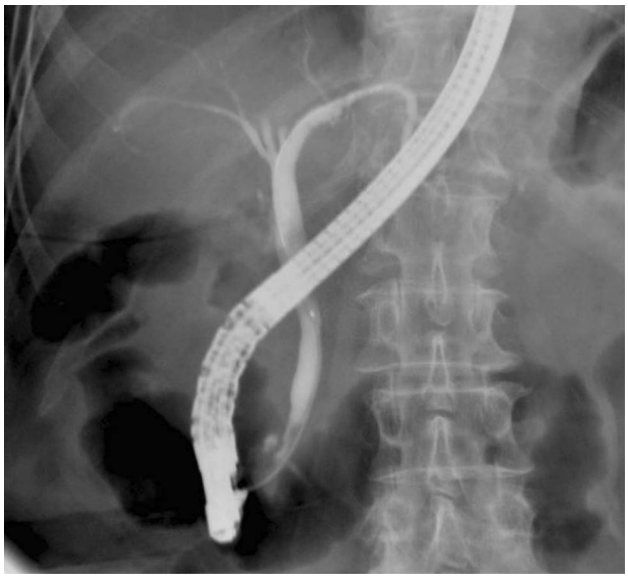

Fig. 3 Cholangiography showed no obvious abnormal findings in the bile duct

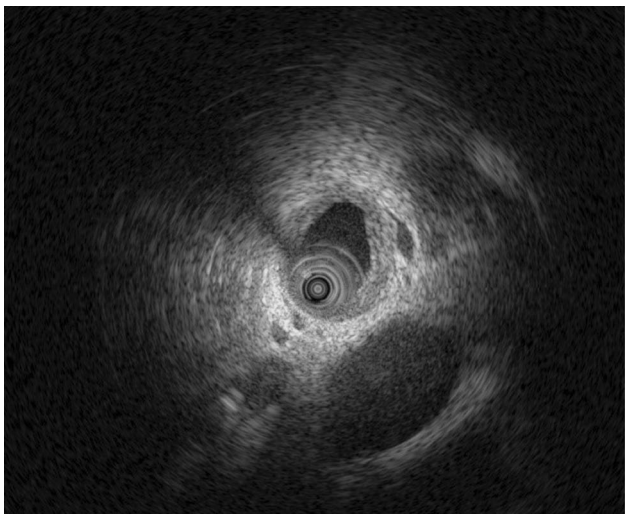

Fig. 4 Intraductal ultrasonography showed a generalized wall thickening

symmetrical and uniform, and the two-layer structure of the wall was preserved (Fig. 4).

Transpapillary bile duct biopsy was performed after the endoscopic sphincterotomy. Three biopsy specimens were taken from the thickened common bile duct using a static jaw (Olympus, FB-45Q-1). Pathological examination revealed that inflammatory cells such as lymphocytes infiltrated the subepithelium of the bile duct, without malignant findings. And $CD8^+$ T cells were predominant compared to $CD4^+$ T cells (Fig. 5), resulting in the diagnosis of atezolizumab-related cholangitis.

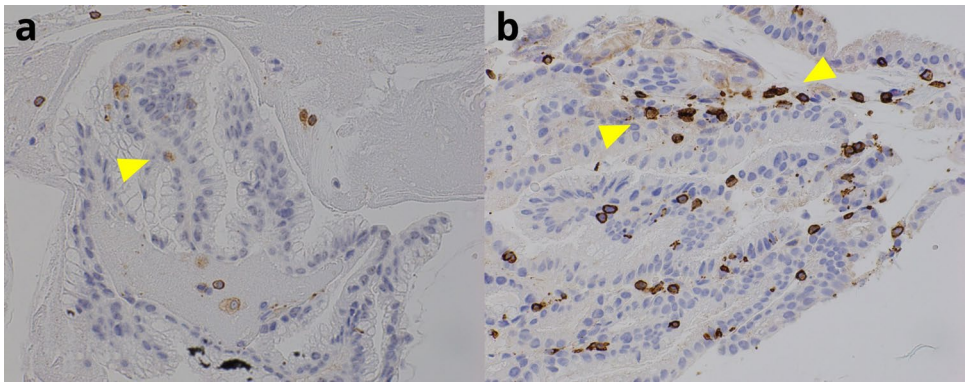

Fig. 5 **a**: Immunohistochemical staining of CD4, ×400. **b**: Immunohistochemical staining of CD8, ×400 $CD8^+$ T cells were predominant compared to $CD4^+$ T cells

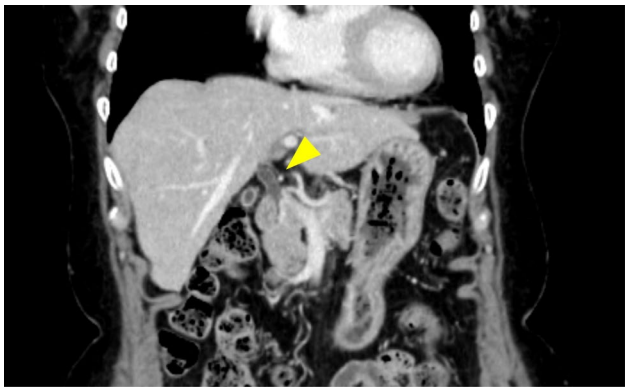

Fig. 6 Bile duct wall thickening disappeared after the discontinuation of atezolizumab

The patient's symptoms were resolved immediately after the discontinuation of atezolizumab. Hepatobiliary enzymes returned to normal 21 days after onset, and bile duct wall thickening disappeared (Fig. 6). At the request of the patient, the treatment plan was changed to best supportive care. Cholangitis relapse did not occur at the 6-month follow-up.

Discussion

Atezolizumab selectively binds to PD-L1 and exhibits antitumor effects by inhibiting the PD-L1 binding to PD-1 and B7.1 [2]. It is widely administered for various cancers and is shown to be effective in unresectable locally advanced or metastatic triple-negative breast cancer in the IMpassion130 phase 3 study [3].

Conversely, irAEs such as liver dysfunction, enteritis, myocarditis, and encephalitis have been reported. The causes of hepatic dysfunction include hepatitis and cholangitis.

In the IMpassion130 phase 3 study, the intention-to-treat population had an increased ALT level in 47 patients and increased ALP level in 10 of 452 patients. ALP has been reportedly elevated in cholestatic liver injury as compared with ALT, suggesting that cholangitis is a less common cause of anti-PD-L1 antibody-induced liver dysfunction than hepatitis. To our knowledge, this is the second case of anti-PD-L1 antibody-related cholangitis reported in English.

Onoyama et al. reviewed 31 patients with PD-1 antibody-related cholangitis. The male-to-female ratio was 21:10, and the median age at onset was 67 (range 43–89) years. The median number of cycles at onset was 5.5 (range 1–27). Abdominal pain (11/31) was the most common symptom, followed by fever (6/31) and jaundice (4/31). Typical images and laboratory findings included bile duct dilatation without obstruction, multiple intrahepatic and extrahepatic bile duct stenoses and homogeneous wall thickening of extrahepatic bile ducts, elevated hepatobiliary enzymes, and normal serum IgG4 levels. Steroid therapy is generally recommended for the treatment of irAE; however, the effect was inadequate in 8 of 26 patients. In addition to steroids, ursodeoxycholic acid, mycophenolate mofetil, tacrolimus, or azathioprine were administered, but these were ineffective [4].

Pathological findings are required to diagnose irAE, characterized by $CD8^+$ T cells predominant infiltration, and hepatitis is characterized by the presence of $CD8^+$ T cells predominant infiltration into the liver parenchyma. Zen et al. reported the presence of $CD8^+$ T cells predominant infiltration into the bile ducts in PD-1 antibody-related cholangitis [5].

Stuart et al. reported a case of hepatitis and cholangitis [6] and suggested that bile duct wall changes should also be evaluated in patients suspected of hepatitis due to high ALT levels compared with ALP levels. This also indicates that not only transpapillary bile duct biopsy but also percutaneous liver biopsy is useful in the pathological diagnosis of ICI-related cholangitis. In ALP-dominant liver injury in which abnormalities cannot be recognized on imaging studies, percutaneous liver biopsy should be considered for ICI-associated cholangitis at the level of the small bile ducts.

When irAE is suspected, liver biopsy or bile duct biopsy may be difficult to perform owing to the patient's general condition. In the present case, cholangitis was the primary diagnosis based on the imaging findings. However, a rare

case of bile duct metastasis from breast cancer has been reported [7], and a bile duct biopsy was performed.

Although the characteristics of PD-1 antibody-related cholangitis are becoming clearer, the clinical features of anti-PD-L1 antibody-related cholangitis remain unclear. The pathogenesis of irAE is not well understood. PD-1 is expressed in lymphoid cells and dendritic cells by cytokine stimulation. PD-L1, on the other hand, is expressed constitutively in organs such as the liver [8]. These differences may lead to differences in irAE by anti-PD-1 antibodies and anti-PD-L1 antibodies.

Nabeshima et al. reported the first case of anti-PD-L1 antibody-related cholangitis in a 77-year-old woman who presented nausea after 13 cycles, and CT and abdominal ultrasonography showed no obvious liver or biliary tract abnormalities. Percutaneous liver biopsy was performed, and pathology showed inflammatory findings with CD8-positive cell infiltration around the intrahepatic bile ducts. Thus, the patient was diagnosed with cholangitis as an irAE. Oral prednisolone was initiated, and hepatobiliary enzymes rapidly improved.

In this case, although MRCP showed no obvious bile duct dilatation or stenosis, CT revealed a slight thickening of the common bile duct wall, and EUS/IDUS revealed a homogeneous bile duct wall thickening of the entire circumference, which finally resulted in a transpapillary bile duct biopsy and a pathologically confirmed diagnosis of anti-PD-L1 antibody-related cholangitis. This case and that of Nabeshima et al.'s report suggest that anti-PD-L1 antibody-related cholangitis may be less likely to show bile duct dilatation and stenosis than anti-PD-1 antibody-related cholangitis. Therefore, the diagnosis of anti-PD-L1 antibody-related cholangitis should not be limited to the findings of bile duct stenosis and dilatation but should also focus on microscopic bile duct wall thickening. Contrast-enhanced CT and EUS/IDUS are effective modalities for detecting subtle bile duct wall changes.

We report a case of anti-PD-L1 antibody-related cholangitis. To diagnose anti-PD-L1 antibody-related cholangitis, microscopic thickening of the bile duct wall should be carefully considered, not only to the findings of bile duct stenosis and dilatation. Careful diagnosis using a combination of multiple modalities (especially contrast-enhanced CT and EUS/IDUS) is required rather than relying on a single modality. In addition, the pathological examination should be performed properly. Clinicians need to inform pathologists about the possibility of irAE and immunostaining for CD4 and CD8 should be performed actively.

Declarations

Conflict of interest Wataru Ichikawa received an honorarium and grant from TAIHO Pharmaceutical and Chugai Pharma.

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