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SHORT REPORT

Ipilimumab associated hepatitis: imaging and clinicopathologic findings

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Summary Ipilimumab is a novel immunomodulator demonstrating promising efficacy in treatment of melanoma and other cancers. The clinical benefit from ipilimumab can be hampered by the immure-related adverse events (irAEs) caused by dysregulation of host immune system. Ipilimumab associated hepatitis is also an important irAE, however, there have been limited descriptions of its clinicopathologic and imaging characteristics. We aim to describe the clinicopathologic and imaging characteristics of 6 patients who were diagnosed as ipilimumab associated hepatitis during the ipilimumab treatment for melanoma. The clinical features of these patients were as follows: (1) severe cases with systemic symptoms and highly increased level of liver function tests (LFTs), and (2) mild asymptomatic cases with mildly increased level of LFTs. In severe cases with ALT >1,000 IU/L, imaging findings were characterized by mild hepatomegaly, periportal edema, and periportal lymphadenopathy, while mild cases showed normal imaging findings. This spectrum of imaging findings in our series was similar to that of common causes of acute hepatitis. Among 3 cases with pathologic specimen, two cases showed severe panlobular hepatitis with prominent perivenular infiltrate with endothelialitis, suggestive of predominant injury to hepatocytes, while the other case showed mild portal mononuclear infiltrate around proliferated bile ductules, suggestive of predominant injury to bile ducts. In summary, ipilimumab associated hepatitis may demonstrate variable imaging findings according to its clinical severity, and histologically may manifest either as a predominant injury to hepatocytes (acute hepatitis pattern) or as a predominant injury to bile ducts (biliary pattern).

Keywords Ipilimumab · Hepatitis · Immune-related adverse events · Imaging · Pathology

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Introduction

Ipilimumab is a monoclonal antibody for cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) which is a key negative regulator of immune response that down-regulates pathways of T-cell activation [1]. Ipilimumab blocks CTLA-4 on activated T cells, enhancing the T-cell immune response to cancer cells [2, 3]. Ipilimumab (Yervoy; Bristol-Myers Squibb, Princeton, NJ) is the first compound proven to improve overall survival in stage IV melanoma [1]. Based on accumulating data on the efficacy of ipilimumab, the US Food and Drug Administration (FDA) approved ipilimumab as monotherapy for metastatic melanoma in 2011 [4].

The clinical benefit from ipilimumab can be hampered by the immure-related adverse events (irAEs) which are unique toxicities of immunomodulators caused by dysregulation of host immune system, as in auto-immune diseases. Two major irAEs are dermatopathies such as skin rash or pruritus which occurred in 47–68 % of treated patients and diarrhea/colitis which occurred in 31–46 % [4]. Immune-mediated hepatitis is also an important adverse event affecting 3–9 % of the patients

treated with ipilimumab [4, 5]. However, there have been limited descriptions of clinicopathologic characteristics and imaging findings of ipilimumab associated immune-related hepatitis [3, 6, 7]. Therefore, the purpose of this study is to describe the radiological findings and clinicopathological features of ipilimumab associated hepatitis.

Materials and methods

This retrospective study was approved by our institutional review board. The computerized search of our radiology database revealed 6 patients diagnosed as ipilimumab associated hepatitis who had available imaging scans at the time of the adverse events. All patients in our series had unresectable or metastatic melanoma and treated with ipilimumab administered intravenously every 3 weeks until adverse events occurred. Clinical data regarding ipilimumab treatment duration, symptoms, laboratory abnormalities, pathologic results of liver parenchymal biopsy specimens, and the treatment for the ipilimumab associated hepatitis were analyzed.

In our series, contrast-enhanced CT of the chest, abdomen and pelvis were routinely performed just before ipilimumab treatment initiation (baseline CT) and 3–4 months after ipilimumab treatment initiation (restaging CTs). All patients in our series underwent abdominal CT and/or additional imaging tests (ultrasonography or MR) due to abnormal liver functions tests (LFTs) during ipilimumab treatment. CT scans were performed by using a 64-row MDCT scanner (Aquilion 64; Toshiba, California) with the following protocols: 0.5 mm collimation, 120 kVp, tube current maximum of 500 mA using dose modulation, 0.5 s gantry rotation time, and a table speed of 26.5 mm per rotation. One hundred milliliters of iopromide (300 mgI/mL; Ultravist 300; Bayer, California) were injected intravenously at a rate of 2–3 mL/s, with a scan delay of 60 s. Imaging findings were evaluated retrospectively and jointly by two radiologists (N.R. and K.W.K., with 12 and 7 years of experience). CT scans performed at the time of LFT abnomalities were compared with the baseline pretreatment CTs and available follow-up CTs to identify the serial change during the clinical course.

Results

Clinical features

The clinical features and imaging findings of the 6 patients (cases 1–6) with ipilimumab associated hepatitis are presented in Table 1. The clinical manifestation of these patients are as follows: (1) symptoms including general weakness, fatigue, nausea and/or mild fever and increased LFTs such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALKP), and/or total bilirubin (T-bil) level (cases 1–4); and (2) asymptomatic increase in AST, ALT, and ALKP (not bilirubin) (cases 5 and 6). The level of LFTs was highly increased in symptomatic patients (case 1–4) with peak ALT >1,000 U/L (reference range <50 U/L) and peak AST >800 U/L (reference range <30 U/L), while asymptomatic patients showed relatively lower level of LFTs with peak ALT 279–367 U/L and peak AST 168–232 U/L (Table 1). Bilirubin level was increased in cases 1–3. Especially, case 1 was regarded as fulminant hepatitis with extremely high LFTs (peak values AST 2412 U/L, ALT 885 U/L, T-bil 19.6). In addition, albumin level had decreased to 2.7 g/dL (reference range 3.7–5.4 g/dL) from initially 4.5 g/dL and PT-INR level had increased to 1.7 (reference range 0.9–1.1), which are markers reflective of liver synthetic function. In the other patients, albumin level and PT-INR were within normal limits.

In all patients, serology for viral hepatitis and antibodies related with autoimmune hepatitis such as antinuclear antibodies, smooth-muscle antibody, mitochondrial antibody, anti-LKM-1, and anti-F-Actin were negative. All patients had an uneventful treatment course until the LFT abnormalities occurred. No patients were exposed to hepatotoxic medication, herbal drugs, or alcohol during the ipilimumab treatment.

The time course of the LFT abnormalities was characterized by a rapid increase in early period and rapid decrease after cessation of ipilimumab and initiation of steroid treatment. Steroid treatment was composed of initial high dose intravenous steroids (solumedrol 120 mg/kg) and subsequent oral steroid (predinosolone) tapering over 2–6 months depending on the patients' condition. In case 1, there was a second peak of abnormal LFTs after initial normalization, which required adjusting the steroid dose and tapering strategy (Fig. 1a). The other cases showed only one peak of abnormal LFTs (Fig. 2). Abnormal laboratory findings including LFTs, albumin and PT-INR normalized after steroid treatment in all patients.

Imaging findings

The patients in our series demonstrated a spectrum of imaging findings from normal to fulminant hepatitis. In case 1–4, severe cases with ALT >1,000 U/L, the common CT findings included mild hepatomegaly, periportal edema, and periportal lymphadenopathy, which were newly apparent on the CT scans at the time of LFT abnormalities (Fig. 1). There was no significant focal lesion, surface nodularity suggestive of chronic liver disease, nor intrahepatic/extrahepatic biliary dilatation. At the time of the acute LFT abnormalities, the CT appearance of the liver parenchyma was diffusely hypoattenuating, compared to the attenuation on prior CT and follow-up CT scans. In case 4, a patient with preexisting liver metastases, CT showed heterogenous liver parenchymal enhancement with geographic areas of low-attenuation, which

Table 1 Characteristics of cases of ipilimumab associated hepatitis

Case No.	Sex/Age	Treatment duration (cycles)	Interval from the last ipilimumab infusion to LFT abnormality	Clinical symptoms	LFT abnormality (AST/ALT/ T-bil*, duration§)	Radiologic findings	Pathologic findings	Follow-up imaging
1	m/63	3	19	Fever (99.4 °F), general weakness, nausea, dizziness	2412/885/19.6, 147 days	CT: Hepatosplenomegaly, periportal edema, periportal lymphadenopathy, diffuse low-attenuation of liver parenchyma. US: Prominent periportal hyperechogenicity, gallbladder wall edema. MR: Prominent periportal T2 hyperintensity	Severe panlobular hepatitis, perivenular infiltrate with endothelialitis	CT: Complete resolution
2	m/44	4	19	Fever (98.7 °F), general weakness, nausea, vomiting.	1059/877/3.6, 75 days	CT: Hepatomegaly, periportal edema, periportal lymphadenopathy, diffuse low-attenuation of liver parenchyma. US: Prominent periportal hyperechogenicity, gallbladder wall edema.	NA†	CT: Complete resolution
3	m/63	3	22	Fatigue	1007/975/7.0, 80 days	CT: Hepatomegaly, periportal edema, periportal lymphadenopathy US: Gallbladder wall edema	Severe panlobular hepatitis, perivenular infiltrate with endothelialitis	CT: Complete resolution
4	m/52	4	17	General weakness, nausea	1343/803/0.7, 94 days	CT: Hepatomegaly, periportal edema, periportal lymphadenopathy, liver parenchymal heterogeneity.	NA	CT: Partial resolution
5	m/82	2	20	Asymptomatic	367/168/0.5, 55 days	CT and US: Within normal limits	Bile ductular proliferation, mixed portal infiltrate around bile ducts	CT and US: Within normal limits
6	f/67	3	9	Asymptomatic	279/232/0.5, 34 days	CT and US: Within normal limits	NA	CT: Within normal limits

*Maximal values of AST, ALT and total bilirubin

§Duration from the last ipilimumab infusion to resolution of LFT abnormality

†*NA* not available

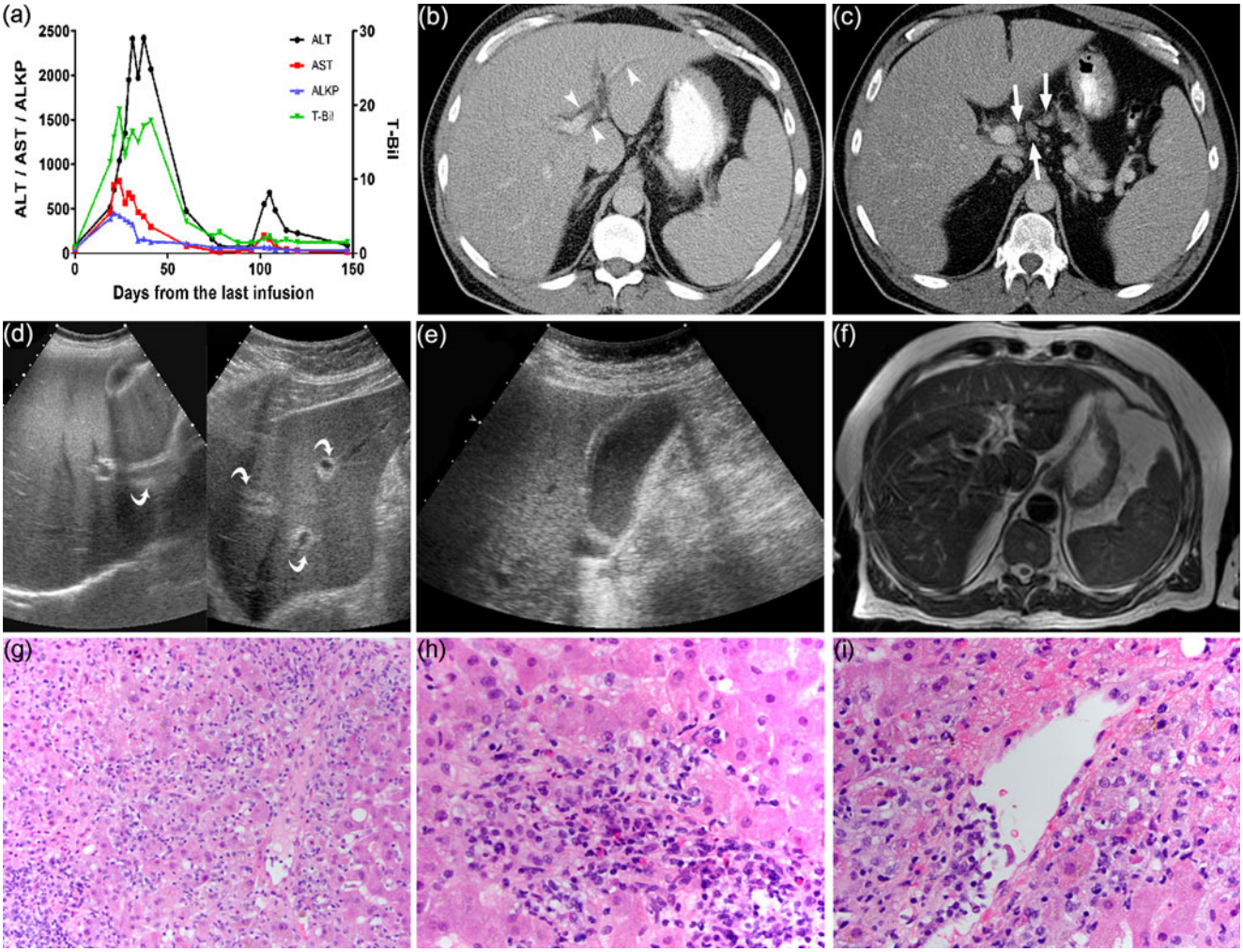

Fig. 1 Sixty three year-old man with fever, nausea and increased LFTs during ipilimumab treatment (case 1). **a** Profile of LFTs. Note the double peaks of LFT abnormalities during steroid treatment. **b**, **c** Axial contrast-enhanced CT images. The size of liver and spleen are increased from prior CT (not shown). New periportal edema [*arrowheads* on (**b**)] and multiple periportal enlarged lymph nodes [*arrows* on (**c**)] are present. **d**, **e** Ultrasonography images demonstrate prominent hyperechogenicity of portal vein wall and periportal space [*curved arrows* on (**e**)] and layered gallbladder wall thickening likely representing gallbladder wall edema (**f**). **f** Axial T2-weighted MR image shows increased T2 hyperintensity in the periportal region, likely representing periportal edema. **g**, **h**, **i** Histopathologic specimens with Hematoxylin and Eosin (H&E) stain show diffuse panlobular hepatitis with scattered plasma cells (**g**, ×40 magnification) and interface hepatitis in portal tracts with predominantly mononuclear cell infiltrate and a few eosinophils (**h**, ×100 magnification). Foci of perivenular lymphoplasmacytic infiltration with endothelialitis were also present (**i**, ×100 magnification)

hampered accurate treatment assessment by obscuring liver metastases and/or mimicking liver metastases (Fig. 2). On follow-up CT scans, findings of hepatomegaly, periportal edema and diffuse low-attenuation liver parenchyma completely resolved, and periportal lymph nodes decreased to subcentimeter size.

Ultrasonography was performed in case 1 and 2, showing prominent echogenicity of portal vein wall and/or periportal space representing periportal edema [8]. Edema of the gallbladder wall was also present (Fig. 1). MRI performed in case 1 demonstrated increased T2 hyperintensity of portal vein wall and/or periportal space, likely representing periportal edema. In contrast, in cases 5 and 6 with relatively milder LFT abnormalities, CT and ultrasound appearances of the liver and gallbladder were within normal limits (Fig. 3).

Pathologic findings

The histopathologic finding from liver biopsy which was performed in three cases (cases 1, 3, and 5) showed two different histological patterns. The case 1 and 3 showed severe panlobular hepatitis with foci of confluent necrosis and prominent perivenular infiltrate with endothelialitis, suggestive of predominant injury to hepatocytes (Fig. 1). In contrast, the case 5 showed bile ductular proliferation and mild mixed portal inflammation with sparse lobular necroinflammatory

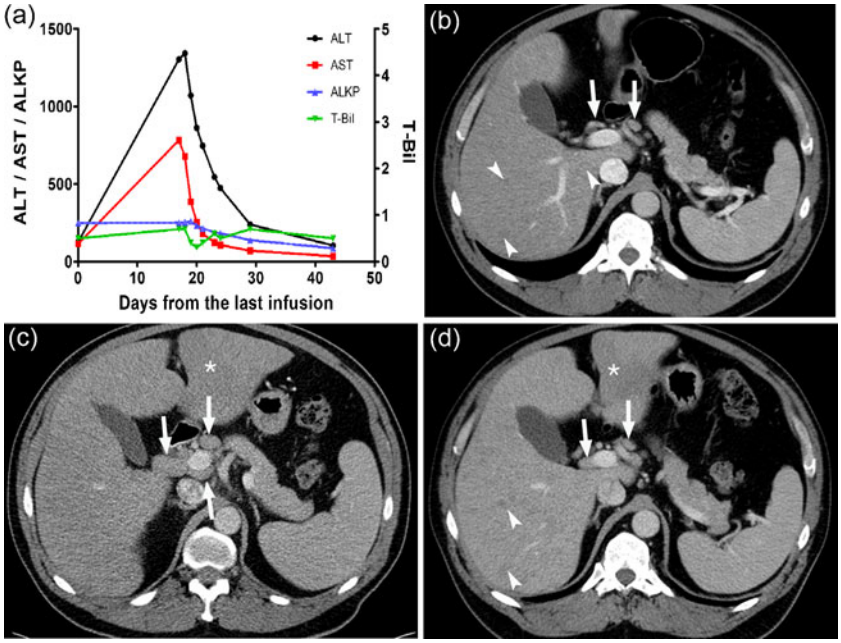

Fig. 2 Fifty two year-old man with general weakness and increased LFTs during ipilimumab treatment (case 4). **a** Profile of LFTs. The level of AST, ALT, and ALKP (not total bilitubin) rapidly decreased after steroid treatment. **b** Axial contrast-enhanced baseline CT before ipilimumab treatment shows multiple small hypodense lesions scattered throughout the liver likely representing hepatic metastases and several periportal small lymph nodes (short axis <1 cm). **c** Axial CT at the time of LFT elevation shows diffusely decreased attenuation of the liver parenchyma which obscures the hepatic metastases. New geographic hypoattenuating areas (*asterisk*) are present, which may mimic liver metastases. Note interval enlargement of periportal lymph nodes (*arrows*). **d** Axial CT 2 months after CT of (**c**) showed multiple discrete hypodense lesions again discernable and interval decrease in size of periportal lymph nodes (*arrows*) and geographic hypoattenuating areas (*asterisk*)

activity. The mononuclear cells in the portal tracts were centered around bile ducts and an eosinophilic infiltrate was prominent in some portal tract, which are nonspecific findings but may raise the possibility of predominant injury to bile ducts (Fig. 3).

Discussion

In our series, the imaging findings of ipilimumab associated hepatitis were variable according to the degree of the laboratory abnormality. In severe cases (cases 1–4), CT findings

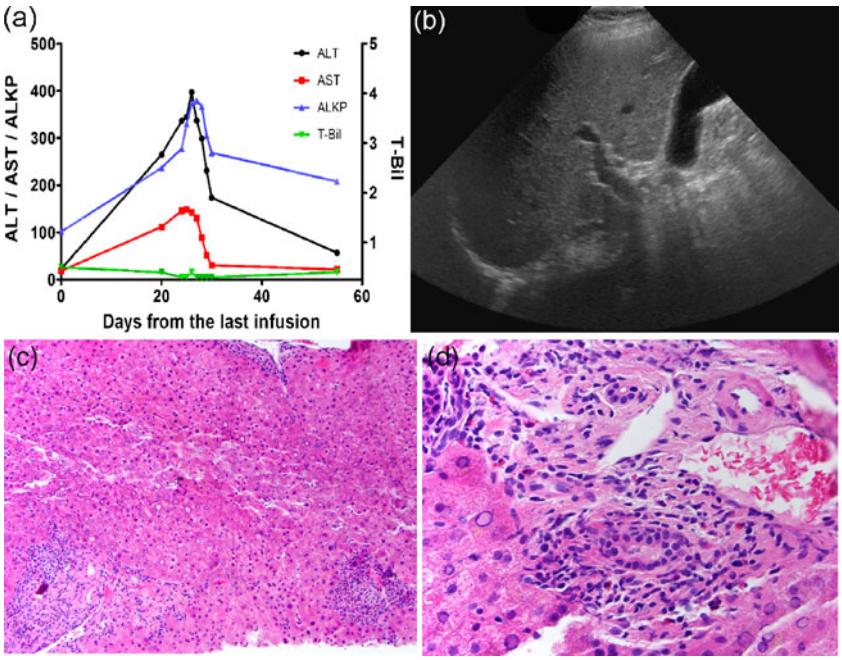

Fig. 3 Eighty two year-old man with asymptomatic increase in LFTs during ipilimumab treatment (case 5). **a** Profile of LFTs. **b** Ultrasonography of the liver and gallbladder is within normal limits. **c**, **d** Histopathologic specimens with H&E stain show portal mononuclear cell infiltration without significant lobular activity (**c**, ×40 magnification) and prominent ductular proliferation (**d**, ×100 magnification). Note that the portal infiltrate are centered around bile ducts (**d**)

were characterized by mild hepatomegaly, periportal edema, diffuse low-attenuation of liver parenchyma, and periportal lymphadenopathy. Ultrasonography findings included prominent periportal echogenicity and gallbladder wall edema. In contrast, the relatively mild cases (cases 5 and 6) showed normal abdominal CT and ultrasonography findings. This spectrum of imaging findings in our series was similar to that of common causes of acute hepatitis (either virally induced or drug induced) [8], even though ipilimumab associated hepatitis is an immune-mediated event causing infiltration of inflammatory cells [4].

Not much is known about the exact mechanism and pathophysiology of ipilimumab associated hepatitis. There have been only 2 pathologic reports (total 5 patients) of ipilimumab associated hepatitis at the time of writing [9, 10]. These five patients of ipilimumab associated hepatitis demonstrated a similar histologic pattern of injury consistent with acute hepatitis such as mixed immune-cell infiltration, interface hepatitis, confluent necrosis, focal necrosis and/or cholestasis, which are nonspecific but similar to findings in autoimmune hepatitis [9]. In our series, a liver biopsy from the cases 1 and 3 also showed an acute hepatitis pattern in the form of severe panlobular hepatitis that is morphologically similar to findings of autoimmune hepatitis. However, a liver biopsy from the case 5 showed mild portal inflammatory around bile ductules suggestive of biliary disorder. Considering these findings in our series and the results of previous studies, ipilumimab hepatotoxicity frequently manifests as a predominant injury to hepatocytes (acute hepatitis pattern) but may manifests as a predominant injury to bile ducts (biliary pattern).

The clinical features of ipilimumab associated immune-related hepatotoxicity are known as generally asymptomatic increases in the levels of aminotransferases (ALT, AST) and/or a relatively mild increase in bilirubin, although some patients had fevers and malaise [4, 5], which are concordant with the clinical features of patients in our series. There was one reported death as a result of fulminant hepatitis [11]. Though being potentially lethal, ipilimumab associated hepatitis has been demonstrated to be reversible and manageable by steroid treatment. During steroid treatment of ipilimumab associated hepatitis, a waxing and waning of LFT abnormalities may be seen and several courses of tapering steroids may be required [4]. In our series, case 1 which was the most severe case showed a second peak of abnormal LFTs requiring a change of the steroid dose and tapering strategy.

Based on the drug mechanism of ipilimumab, which blocks the natural inhibitory signal of CTLA-4 and enhances T-cell activation and its immunostimulatory action, the overall strategy for treatment of ipilimumab associated immune-related adverse events is directed toward reducing the immune reaction and inflammation using steroids [12]. Early detection and treatment of these adverse events is important to avoid significant mortality and morbidity. Most immune-related adverse events are reversible and respond well to steroid treatment. So far, imaging has not been included in the algorithm of diagnosis and management of ipilimumab associated hepatitis, probably because imaging findings are variable and even frequently negative in mild hepatitis, as demonstrated by cases 5 and 6 in our series. We might extrapolate from the results of our series that the majority of ipilimumab associated hepatitis cases of mild to moderate hepatitis show normal imaging. As with acute hepatitis of other etiologies, the role of radiology in patients with suspected ipilimumab associated hepatitis would be in assessment for other diseases that produce similar clinical and biochemical abnormalities, such as extrahepatic cholestasis or diffuse metastatic disease [8].

Ipilimumab is a novel immunomodulator demonstrating promising efficacy in treatment of melanoma and other cancers. In addition, several immunomodulators are awaiting approval [13]. It is therefore important to note the characteristics of immune-related adverse events associated with immunomodulators. Even though the imaging and pathologic findings are non-specific, understanding of the spectrum of imaging and clinicopathologic findings are helpful for management of patients with ipilimumab associated hepatitis. In summary, ipilimumab associated hepatitis demonstrates similar spectrum of imaging findings to those of acute hepatitis of common etiologies and histologically may manifest either as a predominant injury to hepatocytes (acute hepatitis pattern) or as a predominant injury to bile ducts (biliary pattern).

Conflict of interest All authors have nothing to disclose.

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