



Case report

A case of large-cell lung carcinoma successfully treated with pembrolizumab but complicated with cholangitis

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ABSTRACT

Large-cell carcinoma (LCC) of the lung is defined as an undifferentiated non-small cell lung cancer (NSCLC) and accounts for approximately 7.5% of lung cancers. Immune checkpoint inhibitors (ICIs) may be effective for LCC, but there has been no firm evidence due to its low frequency. We herein report an 80-year-old woman with LCC of the lung who was successfully treated with pembrolizumab but developed sclerosing cholangitis as an immune-related adverse event. This case highlights the efficacy of ICIs for LCC as well as the importance of the immediate and detailed management of ICI-related sclerosing cholangitis.

1. Introduction

Historically, large-cell carcinoma (LCC) of the lung accounts for approximately 7.5% of all lung cancers [1]. However, many tumors previously classified as LCC have been reclassified since 2015 WHO classification as adenocarcinoma and squamous cell carcinoma, especially based on an immunohistochemical (IHC) analysis [2]. Therefore, the proportion of LCC is further reduced, making it difficult to establish a standard treatment.

A recent study found that the programmed death-ligand 1 (PD-L1) expression was high in LCC, offering alternative options of targeted therapy [1]. However, about 10%–15% of patients treated with immune checkpoint inhibitors (ICIs) develop grade 3/4 immune-related adverse events (irAEs) [3–5]. Among irAEs, sclerosing cholangitis is rare, and its adequate treatment remains unclear. Prednisolone at 1–2 mg/kg/day has been recommended for the treatment of irAEs [6–8] but being hypo-response to cholangitis [9].

We herein report an 80-year-old woman with LCC of the lung who was successfully treated with pembrolizumab but developed sclerosing cholangitis as an irAE.

2. Case presentation

An 80-year-old Japanese woman was referred to our hospital with a 1-month history of pain near the left shoulder. The patient's medical

history only include lumbar compression fracture. She had no smoking or drinking history.

Her Eastern Cooperative Oncology Group performance status was 0. Her blood pressure was 163/60 mmHg, pulse 79/min, temperature 35.7 °C, respiratory rate 16/min, and O₂ saturation 100% on room air. On a physical examination, her dull pain near the left shoulder worsened on movement. Chest radiography and computed tomography (CT) revealed a mass shadow measuring 50 mm in the upper lobe of the left lung. The mass was in contact with the third to fifth ribs and invaded the fourth rib. A¹⁸F-fluorodeoxyglucose positron-emission tomography (FDG-PET)/computed tomography (CT) showed the accumulation of FDG in this mass, subaortic lymph nodes, left pleural effusion and second lumbar vertebra (Fig. 1). Laboratory tests revealed no elevation of tumor markers (i.e. carcinoembryonic antigen, soluble cytokeratin-19 fragments, pro-gastrin-releasing peptide, and soluble interleukin-2 receptor).

To obtain biopsy specimens of the mass in the upper lobe of the left lung, we performed an ultrasound-guided percutaneous biopsy. Atypical cells with significant anisokaryosis stained dark and eosinophilic reticulum were increased in an alveolar pattern. Spindle-shaped cells were also found and showed atypical mitotic figures. An immunohistochemical study showed focal positive staining for AE1/AE3 and cytokeratin 14 and negative staining for p40, thyroid transcription factor-1, Napsin A, and CEA. Therefore, the patient was diagnosed with LCC (cT3N2M1b; cStage IVA).

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A high PD-L1 expression (Tumor Proportion Score [TPS] $\geq 75\%$) was detected, and the specimen was negative for epidermal growth factor receptor, anaplastic lymphoma kinase, and c-Ros oncogene 1. Treatment with pembrolizumab was initiated as a first-line therapy. Contrast-enhanced whole-body CT performed after eight courses of pembrolizumab treatment showed marked shrinkage of the tumor and disappearance of left pleural effusion.

However, she developed acute liver injury (Grade4; AST 220 U/L, ALT 228 U/L, ALP 2277 U/L) after the 8 courses of pembrolizumab treatment and underwent magnetic resonance cholangiopancreatography (MRCP) and a liver biopsy. MRCP showed no dilation of the intrahepatic bile ducts but did show irregular walls and discontinuous narrowing, and a high signal around the portal vein was detected on T2-weighted imaging (Fig. 2A, B). A pathological examination of the liver biopsy specimen showed slightly enlarged portal vein areas, infiltration of chronic inflammatory cells, such as small lymphocytes, and bile duct components of the juvenile epithelium covering large and small discordant nuclei. On the lobules, binuclear cells, mild sinusoid dilatation, very mild large drop statues, and necrotic inflammatory reaction of necrotic small cells, including neutrophils, were observed (Fig. 2C). Blood testing showed normal levels of the serum immunological markers (i.e. anti-nuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, and IgG4). Based on these results, the patient was diagnosed with sclerosing cholangitis.

Treatment was started with 40 mg/day (1 mg/kg/day) of prednisolone, and reduced to 30 mg/day 2 weeks later and further to 25 mg/day 5 days later. During the therapy, her liver injury temporarily improved to Grade 1 (AST 27 U/L, ALT 38 U/L, ALP 535 U/L) but worsened (AST 43 U/L, ALT 58 U/L, ALP 584 U/L) at 1 month after the introduction of corticosteroids, so the dose was increased to 30 mg/day with immunosuppressant (azathioprine, 50 mg/day). Her liver injury further worsened (AST 60 U/L, ALT 77 U/L, ALP 731 U/L), so additional steroid pulse therapy (1000 mg/day of methylprednisolone for 3 days) was initiated. Her liver injury improved, and a repeated liver biopsy confirmed the pathological improvement of cholangitis six months after the onset of this condition (Fig. 3), which enabled gradual corticosteroid reduction and immunosuppressant discontinuation. In addition, her lung cancer has not relapsed in the one year since the discontinuation of pembrolizumab (Fig. 4).

3. Discussion

Lung cancer is divided into small-cell lung cancer and non-small-cell lung cancer (NSCLC). LCC is the third-most common subtype of NSCLC after squamous cell carcinoma and adenocarcinoma [1]. According to the 2015 WHO classification of lung tumors, LCC is defined as a 'resected tumors that lack any clear morphologic or immunohistochemical differentiation towards small cell carcinoma, adenocarcinoma or squamous cell carcinoma' [2]. Due to the small number of LCC cases, there is still no consensus concerning useful treatments for advanced LCC. One study reported that 59 of 789 NSCLC cases were LCCs, which amounts to about 7.5% of cases. That study showed that adenocarcinoma had a high probability of a genetic mutation, while many LCC cases had a high PD-L1 expression rate [1]. We experienced a case of LCC with a high PD-L1 expression showing a complete response to pembrolizumab, so ICIs may be effective for LCC patients.

Approximately 10%–15% of patients treated with ICIs may develop grade 3/4 irAEs [3–5]. Common irAEs include rash and diarrhea, accounting for 4%–11% and 8%–11% of cases, respectively [10]. Among irAEs, biliary system complications are rare (incidence: 1%–3%), and their clinicopathological features and ideal treatment remain unclear [11,12]. Kawakami et al. revealed that nivolumab-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 enzymes ALP and γ GTP compared to the hepatic enzymes AST and ALT; (4) normal or reduced levels of the serum immunological markers (i.e. anti-nuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, and IgG4); (5) the pathological finding of CD8⁺ T cell infiltration around the portal area on a liver biopsy; and (6) a moderate to poor response to steroid therapy [9]. Our patient met all of these items except for (5).

Two-week treatment with prednisolone at 1 mg/kg/day has been recommended for ICI-related sclerosing cholangitis. After the initial treatment, a repeated liver biopsy is recommended to confirm any significant lymphocytic/neutrophilic infiltrate in the tissue. If inflammation remains, escalation of prednisolone to 2 mg/kg is recommended. If no inflammation remains, dose tapering of prednisolone to 5 mg/week is recommended [13]. Ursodeoxycholic acid (UDCA) and the early prescription of bezafibrate before liver fibrosis progresses are reported to be

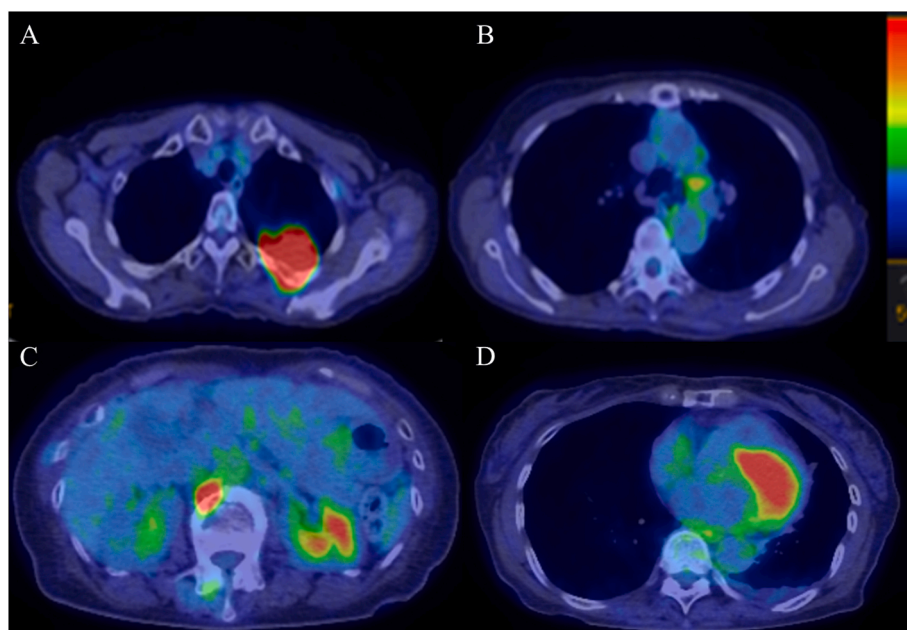


Fig. 1. ¹⁸F-FDG-PET CT. The abnormal accumulation of FDG was detected in a mass in the left upper lobe (A), subaortic lymph nodes (B), second lumbar vertebra (C), and left pleural fluid (D) with high metabolic activity (SUV_{max}: 1.55–9.80).

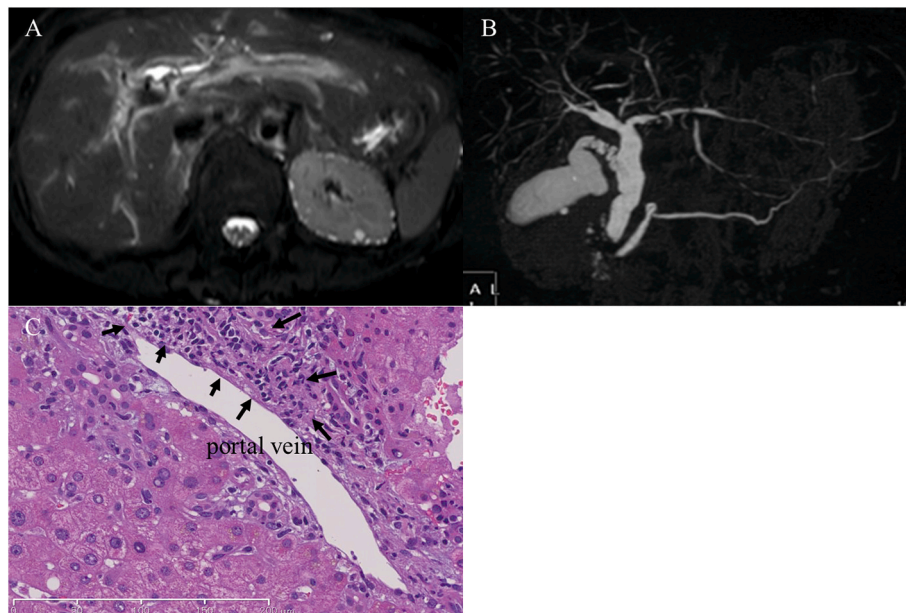


Fig. 2. MRI and pathological findings of the liver. MRI showed no intrahepatic bile duct dilatation, but biliary wall irregularity and discontinuous narrowing of the bile duct were noted (A,B). A liver biopsy showed chronic inflammatory cell infiltrate and juvenile epithelial bile duct around the slightly enlarged portal vein area (C).



Fig. 3. Pathological findings of the repeated liver biopsy specimen after steroid pulse therapy. Chronic inflammatory cells slightly were observed around the portal vein area but showed an improving trend (D).

effective [14]. Mycophenolate mofetil and infliximab were also reported as additional treatments [13,15]. Our patient first received systemic corticosteroid therapy and later added azathioprine, but her liver injury did not fully improve. Therefore, steroid pulse therapy was initiated, which was successful.

To our knowledge, 10 cases of pembrolizumab-related cholangitis have been reported in the English literature (Table 1) [16–22]. The underlying malignancies were melanoma/NSCLC/mesothelioma/bladder cancer in 2/5/1/2 cases, respectively. An average of 6 cycles (range, 1–17) of pembrolizumab was administered before the onset of cholangitis. Treatments for cholangitis were as follows: only

discontinuation of pembrolizumab, 1 case; UDCA only, 1 case; high dose of prednisolone (≥ 1 mg/kg/day) with or without UDCA, 5 cases; high dose of prednisolone (≥ 1 mg/kg/day) with immunosuppressant (i.e. mycophenolate mofetil), 2 cases; steroid pulse therapy with methylprednisolone followed by prednisolone maintenance therapy, 1 case; and steroid pulse therapy with methylprednisolone followed by prednisolone maintenance therapy with immunosuppressant (i.e. azathioprine), 1 case (our patient). The effectiveness of these therapies has been reported to be poor to moderate. Given the clinical course of our patient, steroid pulse therapy is considered an effective option. The appropriate duration of treatment for cholangitis is unknown. In the previous reports, steroid reduction is often started when liver enzymes return to their pre-cholangitis levels, and steroids are then terminated over the next 4 weeks or more. We did so in the present case.

4. Conclusion

Herein we reported an extremely rare case with LCC of the lung who was successfully treated with pembrolizumab but developed sclerosing cholangitis as an irAE. This case highlights the efficacy of ICI for LCC as well as the importance of the immediate and detailed management of ICI-related sclerosing cholangitis.

Role of study

Kosuke Tsuruno: Data collection, Interpretation of data, Writing of the manuscript.

Kazunori Tobino: Writing of the manuscript.

Mitsukuni Sakabe: Data collection.

Takafumi Kawabata: Data collection.

Yuri Hiramatsu: Data collection.

Takuto Sueyasu: Interpretation of data.

Kohei Yoshimine: Interpretation of data.

Declaration of competing interest

All the authors have no conflict of interest about this case report.

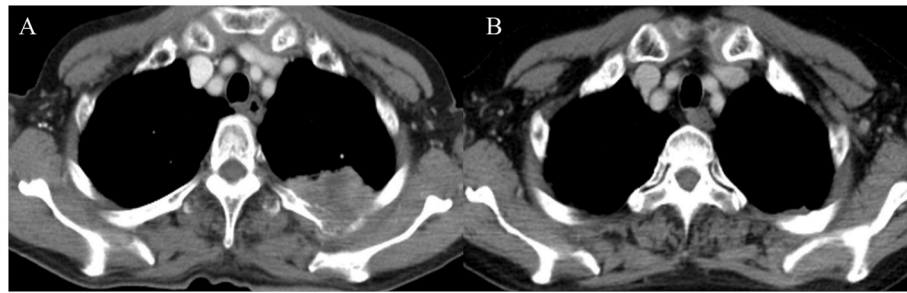


Fig. 4. Chest CT findings before the treatment (A) and one year after the discontinuation of pembrolizumab.

Table 1

Previously reported cases of pembrolizumab-related sclerosing cholangitis and our case.

Author	Age/ Sex	Primary disease/ Cycles until onset	AST/ ALT ALP/ γGTP (U/L)	Symptoms	Biliary stenosis/ dilation	Hypertrophy of biliary tract	Pathological findings	Treatment/response
Ogawa et al. [16]	73/ M	Melanoma/NA (3 mo)	58/77 1111/ 461	None (liver dysfunction)	Multiple/+	Diffuse	Bile duct: Destruction of epithelium, fibrosis with CD8 ⁺ T cell infiltration in submucosa	Discontinuation of Pembrolizumab/-
Koya et al. [17]	66/ M	NSCLC/5	313/ 296 2241/ 868	Epigastric pain	Intrahepatic bile duct/+	Diffuse	Liver: CD8 ⁺ T cell and eosinophil infiltration in the periportal zones, Bile duct: CD8 ⁺ T cell infiltration and fibrosis in submucosa tract with bile duct loss	1st UDCA (900 mg) + bezafibrate (400 mg), 2nd m PSL (0.5 g) followed by PSL (1 mg/kg), Biliary drainage/Poor
Doherty et al. [18]	49/F	Melanoma/1	961/ 1536 2237/ 2094	Jaundice	NA/-	NA	Liver: Severe steatohepatitis, absence of bile ducts	1st PSL (1 mg/kg), 2nd PSL + UDCA (NA) + MMF (2 g)/ Poor
Doherty et al. [18]	76/ M	Mesothelioma/1	NA/ >500 >700/ NA	Jaundice	NA	NA	Liver: Attenuated bile duct, cellular and canalicular cholestasis in parenchyma	mPSL (2 mg/kg) + cholestyramine (NA) + MMF (1 g) + UDCA (NA)/ Poor
Fouchard et al. [19]	61/ M	NSCLC/17	NA/ >100 >400/ >1400	None (liver dysfunction)	NA	NA	NA	PSL (1 mg/kg)/Moderate
Zen et al. [20]	68/ M	NSCLC/NA (5.5 mo)	67/68 2107/ 279	Abdominal pain, vomiting	NA/-	Diffuse	Liver: Cholangiopathologic change, CD8/CD4 ratio 12:7, Bile duct: Lymphocyte, eosinophil and plasma cell infiltration	PSL (50 mg)/Moderate
Zen et al. [20]	67/ M	NSCLC/NA (1 mo)	198/ 233 1540/ 332	Fever, malaise	NA/-	Diffuse	Liver: Lobular hepatitis with cholangiopathologic change, CD8/CD4 ratio 17:2	PSL (50 mg)/Moderate
Onoyama et al. [21]	61/ M	Bladder cancer/5	91/65 1683/ 159	Fever	-/+	Diffuse	Bile duct: Inflammatory cell infiltration	PSL (1 mg/kg) + UDCA (600 mg)/Moderate
Onoyama et al. [21]	89/ M	Bladder cancer/4	245/ 124 1245/ 114	None (liver dysfunction)	-/+	Diffuse	Bile duct: Neutrophil and lymphocyte infiltration	UDCA (600 mg)/-
Onoyama et al. [21]	63/ M	NSCLC/7	184/ 254 1783/ 452	None (liver dysfunction)	-/+	Diffuse	Bile duct: Inflammatory cell infiltration	PSL (1 mg/kg) + UDCA (600 mg)/Moderate
Our case	80/F	Large cell cancer/8	220/ 228 2277/ 953	None (liver dysfunction)	+/-	Diffuse	Liver:chronic inflammatory cell infiltrate and juvenile epithelial bile duct around slightly enlarged portal vein area	1st PSL (40mg)+ azathioprine (40mg), 2nd mPSL (1.0g) followed by PSL (30mg/kg)

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