European Review for Medical and Pharmacological Sciences 2023; 27: 1436-1442

Could immune-related hepatitis rapidly progress to immune-related cirrhosis?

Y.-N. LEI[1,3], X.-Y. LI[2,3], G. GAO[1,3], W.-Y. WANG[4], Z.-Y. LIANG[4], Y.-S. WANG[1,3]

[1]Thoracic Oncology Ward, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China
[2]Clinical Trial Center, NMPA Key Laboratory for Clinical Research and Evaluation of Innovative Drugs, West China Hospital, Sichuan University, Chengdu, Sichuan, China
[3]State Key Laboratory of Biotherapy, Sichuan University, Chengdu, Sichuan, China
[4]Department of Pathology, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Yanna Lei and Xiaoyu Li contributed equally to this work

Abstract. – BACKGROUND: Immune-related hepatitis is one of the prevalent adverse events associated with immunotherapy, especially immune checkpoint inhibitors (ICIs). For patients without a history of liver disease, autoimmune disease, or alcohol consumption, it is not clear whether immune-related hepatitis could rapid progress to immune-related cirrhosis.

CASE REPORT: We report the case of a 54-year-old female with stage IIIB primary pulmonary lymphoepithelioma-like carcinoma (PLELC) diagnosed with immune-related hepatitis. After 15 months, a liver biopsy demonstrated the rapid progression of liver cirrhosis although systematic corticosteroid administration.

CONCLUSIONS: Long-term immune activation caused by ICIs may exacerbate the process of cirrhosis. Great attention should be paid to the rapid progression to liver cirrhosis of immune-related hepatitis in the clinic.

Key Words:
Immune checkpoint inhibitors, Immune-related hepatitis, Liver cirrhosis, Primary pulmonary lymphoepithelioma-like carcinoma, Corticosteroid.

Introduction

The efficacy of immune checkpoint inhibitors (ICIs), which blocks cytotoxic T lymphocyte associated protein-4 (CTLA-4) and programmed death-1 (PD-1) axis, has led to their widespread use for the management of cancers[1,2]. However, a series of immune-related adverse events (irAEs) have been recognized[3,4] with the widely clinical administration of ICIs. IrAEs can occur in any organ and the most reported[5] side effects of liver is immune-related hepatitis. However, immune-related hepatitis rapid progression to immune-related cirrhosis has not been reported to date. Pembrolizumab is a humanized monoclonal anti-PD-1 antibody that is effective as a monotherapy and combination therapy in many cancers[6]. Pulmonary lymphoepithelioma-like carcinoma (PLELC) is an uncommon, Epstein-Barr virus (EBV) associated, non-small-cell lung cancer (NSCLC)[7,8]. The incidence of PLELC is 0.7% of all NSCLC cases[9] and no specialized treatment guidelines have been established. Recent study[10,11] showed that ICIs may be a promising strategy for advanced PLELC, but large clinical trials are warranted to obtain more evidence to confirm the efficacy.

Herein, we present a case of pembrolizumab-induced hepatitis rapid progression to immune-related cirrhosis and highlight the significance of clinic and imaging manifestations which help prompt diagnosis as well as establish a specific treatment.

Case Presentation

A 54-year-old Chinese female patient presented at our hospital due to repeated cough in June 2019. Computed tomography (CT) revealed a soft tissue mass shadow (3.1 cm × 2.9 cm) in the hilum of the right middle lobe with mediastinal and right hilar lymphadenopathy (Figure 1A-B). Endobronchial ultrasound (EBUS) was performed in 4R lymph node areas and the pathology results confirmed non-small cell carcinoma, lymphoepithelioma-like carcinoma (Figure 2A). Immunohistochemistry staining

Corresponding Author: Yongsheng Wang, MD; e-mail: wangys@scu.edu.cn

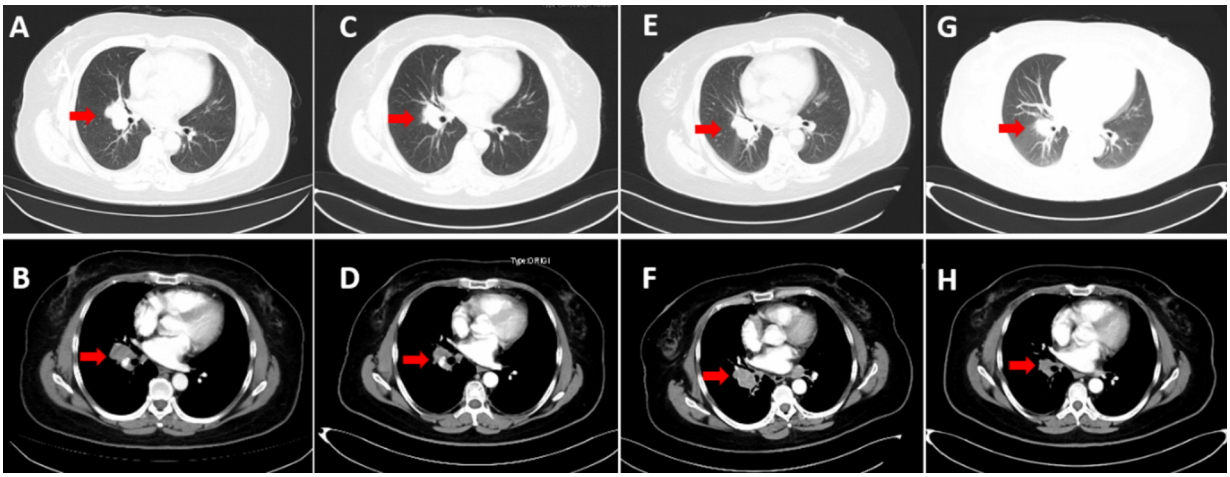

Figure 1. Computed tomography (CT) scan of the lungs before and after treatment. **A-B**, Before treatment, July 2019. **C-D**, After 2 cycles of pembrolizumab and chemotherapy, August 2019 (stable disease in objective response assessment). **E-F**, Disease progression, April 2020. **G-H**, After 5 cycles of treatment with gemcitabine plus cisplatin, October 2020.

showed: PCK (-), CK5/6 (-), P63 (-), TTF-1 (-), CK7 (-), EBER-ISH (+) (Figure 2B). And Ki-67 was 60%. The programmed cell death ligand 1 (PD-L1) expression was 90% (PD-L1 expression was detected by immunohistochemistry staining with an anti-human PD-L1 monoclonal antibody 22C3) (Figure 2C-D). Combined with medical history and auxiliary examination, the patient

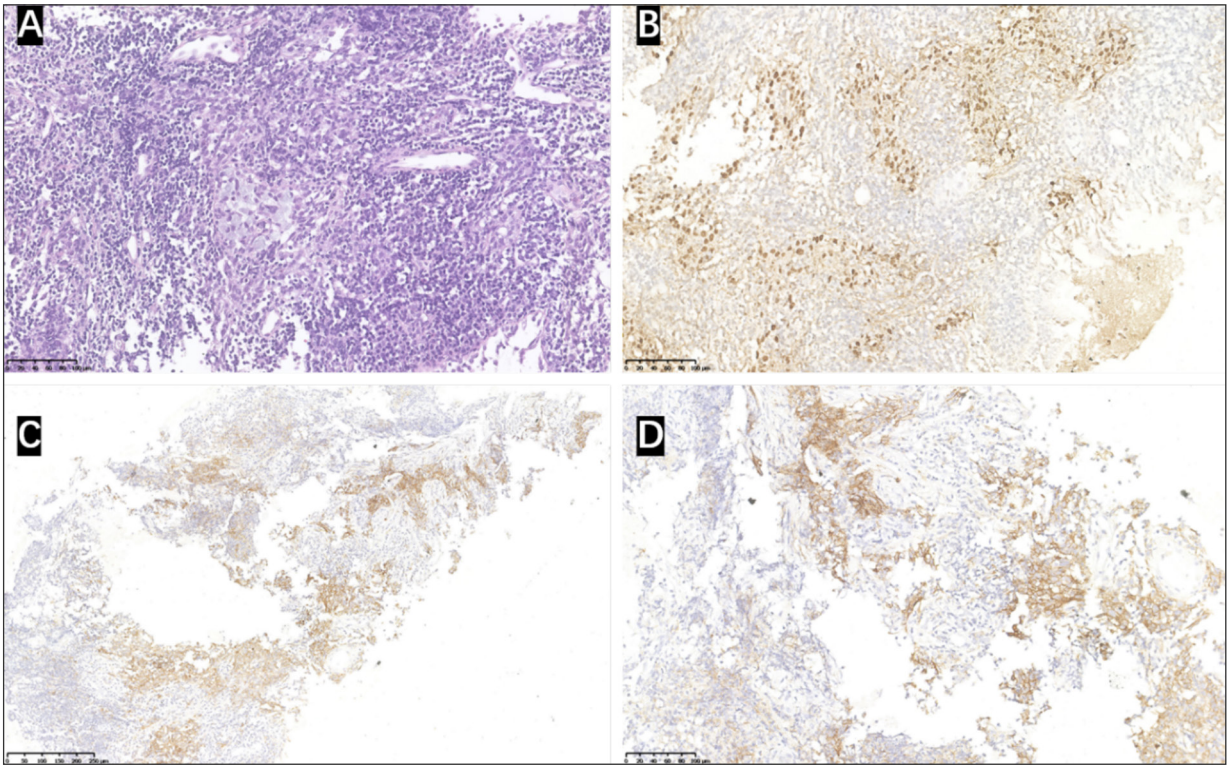

Figure 2. Microscopic findings of the 4R lymph node biopsy. **A**, Histological examination reveals primary pulmonary lymphoepithelioma-like carcinoma (magnification ×20). **B**, *In situ* hybridization showing tumor nuclei positive for Epstein-Barr Virus-encoded RNA (magnification ×20). **C-D**, Immunohistochemical staining for PD-L1 expression was 90% (**C**: magnification ×10; **D**: magnification ×20).

was formally diagnosed stage IIIB PLELC and was not considered for surgery. She had no history of autoimmune disease, liver disease, or alcohol consumption. Virology screen and autoantibody screen were negative.

The patient received systemic treatment in July 2019 (pembrolizumab 200 mg, albumin-bound paclitaxel and carboplatin, q3w). Stable disease (SD) achieved after two cycles of treatment, and she was well-tolerated with this regimen (Figure 1C-D). However, the patient was diagnosed with hypothyroidism and laboratory tests showed increased level of aminotransferase [ALT: 136 IU/L (normal range: 0-40 IU/L); AST: 143 IU/L (normal range: 0-35 IU/L)] as well as myocardial enzymogram (Troponin-T: 153.6 ng/L, normal range: 0-14 ng/L) on admission for third cycles of treatment. Then multisystem irAEs were diagnosed after a multidisciplinary review. Considering the irAEs involved in multiple organs (liver, heart, lung, and thyroid), pembrolizumab and chemotherapy agents were ceased. High dose (2 mg/kg IV daily) of methylprednisolone was timely used from August 2019 and tapered over a six-month period. Corticosteroids were stopped in April 2020. At the same time, a CT scan revealed disease progression (Figure 1E-F). In addition, multiple metastatic lesions were present in the liver (Figure 3C). Gemcitabine plus cisplatin were adopted as second-line treatment. The patient received 5 cycles of treatment from May 2020 to October 2020 (Figure 1G-H). Regular image review of chest CT suggested a sustained status of SD. However, the patient developed gradual distention of the abdomen and respiratory distress in November 2020. Abdominal ultrasound (US) at a local hospital in December 2020 suggested gross ascites. The ascites was not well controlled although the patient received abdominal paracentesis and repeated intraperitoneal cisplatin perfusion. Then, the patient received anlotinib, a multi-target antiangiogenic-tyrosine kinase inhibitor, on a 12 mg qd, 2 weeks on and 1 week off schedule, as third-line therapy. However, anlotinib failed to control the formation of ascites.

The patient was admitted to our hospital again on March 30, 2021, due to increased abdominal girth and shortness of breath. Large-volume paracentesis with albumin supplementation were given and massive ascites reduced rapidly. Repeated cytological examinations of ascitic fluid revealed lymphocytes infiltration without malignant cells. However, re-accumulation of ascitic fluid was observed. 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET/CT) showed an abnormally high uptake on the tumorous lesion in the hilum of the right lobe with mediastinal

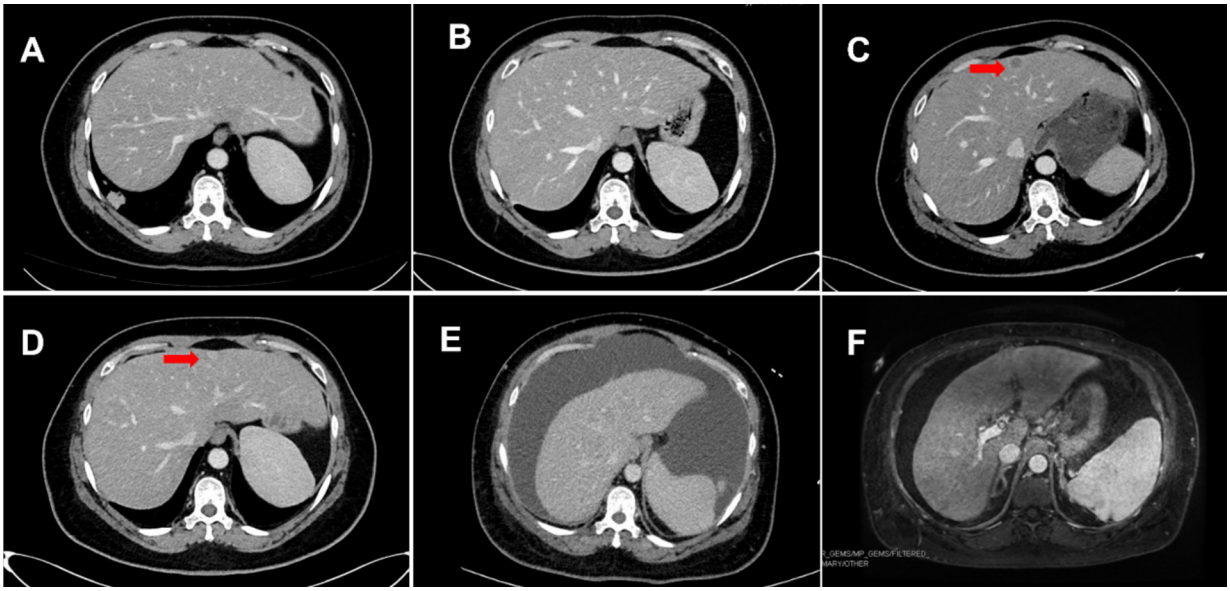

Figure 3. Computed tomography (CT) and magnetic resonance imaging (MRI) scan of the liver during treatment. **A**, Before treatment, July 2019. **B**, After 2 cycles of pembrolizumab and chemotherapy, August 2019. **C**, Disease progression and liver metastases, April 2020. **D**, After 5 cycles of treatment with gemcitabine plus cisplatin, October 2020. **E**, The patient was admitted to our hospital again in March 2021. **F**, After TIPS, May 2021.

lymphadenopathy. Marked accumulation was not found in other sites, confirming there was no evidence of metastasis in the abdominal cavity and liver. In addition, liver cirrhosis, splenomegaly, and ascites were also reported by PET/CT. The patient strongly requested to figure out the possible reasons, so we performed further examination. Liver stiffness, assessed by shear wave elastography, was 39.0 kPa (the mean normal liver tissue stiffness ranged from 2.8 to 7.4 kPa). Subsequently, transjugularl liver biopsy and hepatic venous pressure gradient (HVPG) confirmed the diagnosis of cirrhosis. Liver biopsy showed mild chronic inflammation and interface hepatitis. Lymphocytic and plasma cell infiltration could be seen in the portal area (Figure 4A). Additionally, the MASSON trichrome staining showed fibrous tissue hyperplasia, enlargement of the portal area, fibrous septum formation and the hepatic lobules were partially separated (Figure 4B). Immunohistochemistry staining showed: HBsAg (-), HBcAg (-), CD38 (+ partial), IgG4 (-) (Figure 4C-F). Autoimmune hepatitis or drug-induced liver injury could not be ruled out. All workups for viral hepatitis, autoimmune diseases with liver involvement and alcohol-associated as well as fatty-associated cirrhosis were negative. Combined with the treatment history on ICIs, finally, cirrhosis was hypothesized to be due to pembrolizumab. Transjugular intrahepaticportosy stemicshunt (TIPS) was given to alleviate portal hypertension and control refractory ascites. In addition, methylprednisolone 1 mg/kg/day was started and then gradually tapered down. The patient demonstrated marked improvement within the timely treatment. Symptomatic relief further confirmed our diagnosis. All other possible causes of liver cirrhosis were excluded, and the diagnosis of immune-related cirrhosis was confirmed (Figure 5A).

Discussion

The advent of ICIs has ushered in a new era in cancer management. ICIs could prevent tumor away from immune surveillance and cause an optimum activation of cytotoxic T cells to kill cancer cells effectively. ICIs have dramatically improved the survival of patients when used in both first and subsequent-line settings[12,13]. However, it may lead to a wide spectrum of immune-related adverse events that mimic autoimmune disorders in any organ and any tissue such as dermatological, gastrointestinal, hepatic, endocrine and other systems[14,15]. Liver immune-related events mainly refer to immune-related hepatitis. The incidence of immune-related hepatitis was 5-10% in ICI monotherapy and up to 30% in combination therapy[16,17]. Evidence[18] showed that the resident Kupffer cells and neutrophils were correlated with liver toxicity caused by immunotherapy. The

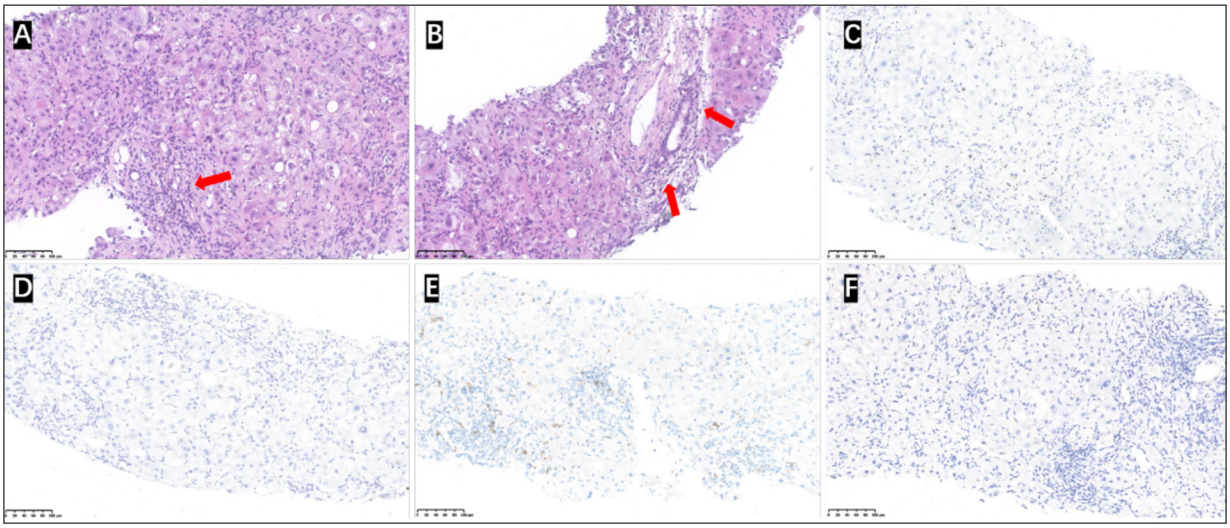

Figure 4. Histological findings of a biopsy sample from liver (magnification ×20). **A**, Numerous lymphocytes infiltrated into the portal area (*arrow*). **B**, Hepatic lobules were partially separated by fibrous septum (*arrow*). **C-F**, Immunohistochemistry staining showed: HBsAg (-), HBcAg (-), CD38 (+ partial), IgG4 (-) (magnification ×20).

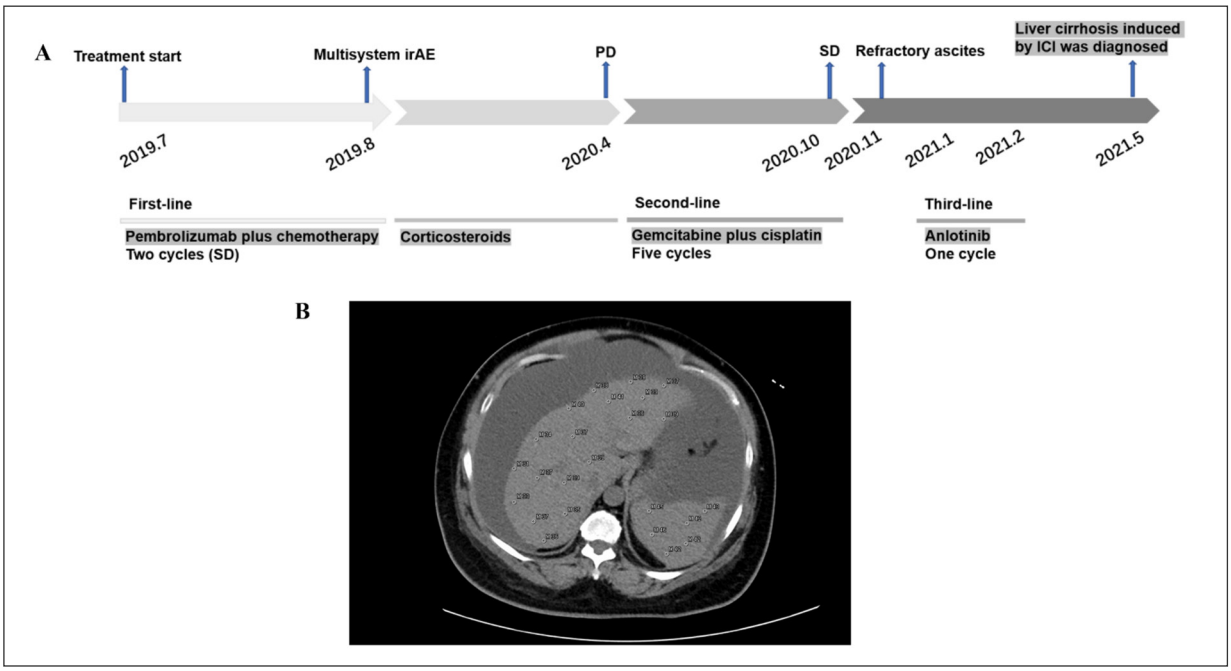

Figure 5. **A**, Timeline scheme of major clinical events of the patient since diagnosis. **B**, The liver density diffusely decreased and was lower than spleen when she was admitted to our hospital again on March 2021.

majority liver injury induced by ICIs are asymptomatic[19]. Clinically, hepatotoxicity can present with a range finding, from the elevation of serum transaminases or bilirubin levels to hepatobiliary disease such as autoimmune hepatitis, cholangitis, jaundice and liver failure[20,21]. Although irAEs can occur in any organ, hepatotoxicity is a common side-effect of ICIs. Immune-related cirrhosis remains a rare complication which has not previously been reported.

The histopathological characteristics of patients with immune-related hepatitis is not clear and the current descriptions are mostly based on the findings from case reports. Distinct histological patterns of hepatitis were discovered between treated with anti-PD-1/PD-L1 mAb or treated with anti-CTLA4 mAb[22]. Granulomatous hepatitis, fibrosis, and central venous dermatitis were showed in patients who received anti-CTLA4 treatment. However, hepatotoxicity related to anti-PD-1/PD-L1 mAb characterized by lobular hepatitis. Our histological findings are more similar with the autoimmune hepatitis which presented with plasma cell infiltration, severe interface hepatitis and piecemeal necrosis[23]. The imaging findings suggestive of liver cirrhosis and the liver biopsy as well as HVPG provided further evidence. The liver density changed according to the etiology as well as the severity of the liver disease such as liver cirrhosis[24]. The density of normal liver tissue was higher than the spleen, but the liver density in liver cirrhosis was lower than spleen in general. In our patient, the density of liver diffusely decreased and lowered compared to the spleen which also contributed to the diagnosis (Figure 5B). Immune associated hepatitis may demonstrate variable imaging appearance according to its severity. Mild cases showed nonspecific imaging findings and severe cases showed hepatomegaly, periportal edema, as well as periportal lymphadenopathy[25,26], but distinct CT manifestations were shown in patients with cirrhosis such as ascites, liver shrinkage, and splenomegaly.

The cirrhosis is a consequence of long standing excessive fibrogenesis which usually takes a long time. Hepatitis virus infection, alcohol consumption, fatty as well as autoimmune disease are major risk factors for liver cirrhosis. However, immune activation and inflammation caused by ICIs may also contribute to the progression of cirrhosis. EBV infection is one of the causative agents of head and neck cancers, such as NPC[27]. Studies[28] also reported that EBV is associated with liver disease. Research[28] revealed that liver injury will aggravate in patients with EBV-infected. Primary liver cancers are associated with

a higher risk of immune-related hepatotoxicity compared with other solid tumors such head and neck cancer[21]. Secondary liver tumor may also directly accelerate the evolution of the disease. In our cases, the liver function returned to the normal range after timely treatment when diagnosed with immune-related hepatitis and PET/CT did not show any high metabolic foci in liver. All other possible causes of liver cirrhosis were excluded and the immune-related cirrhosis was mainly related to the immunotherapy.

The observations of this case challenge the present recommendations concerning the management of immune-related hepatitis. In most cases, the immune-related hepatitis is not severe, and corticosteroids might not be necessary for the treatment of some patients[22,29]. The spontaneous hepatitis resolution was observed in some patients and a minority of them were even rechallenged with immunotherapy after an improvement from immune-induced hepatitis. Although systematically corticosteroid administration, the patient in our case still eventually developed liver cirrhosis after 15 months. It is important to diagnose and treat patients with ICI-induced hepatitis earlier by multidisciplinary therapies. Corticosteroids and immunosuppressants are the main treatment choice for liver injury related to ICIs. However, the outcomes are often unsatisfactory[30,31]. The corticosteroid is extremely debatable due to the adverse events and its negative influence on the efficacy of immunotherapy[29,30]. For the immune-related cirrhosis, the treatment strategy also should be reconsidered.

Conclusions

This report describes the first case of immune-related hepatitis rapid progression to liver cirrhosis in a patient with lymphoepithelioma-like lung cancer who was treated with pembrolizumab. Excluding the reason of viral, alcoholic, fatty, autoimmune liver disease and infection, the liver cirrhosis was considered as correlated with immune-related hepatitis. Beware of the cirrhosis followed by immune-associated hepatitis was rational. Long-term immune activation caused by ICIs may exacerbate the process of cirrhosis. Identification and monitoring of rapid progression should become an important aspect in oncologic care.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Approval

Not applicable.

Informed Consent

The patient provided the informed consent to publish this case.

Funding

This work was supported by National Natural Science Foundation of China (Grant No. 81872489, 82073369), the China Postdoctoral Science Foundation (No. 2020M683323) and the Natural Science Foundation of Sichuan Province (2022NSFSC1412).

Authors' Contribution

Yongsheng Wang: Conceptualization. Yanna Lei, Xiaoyu Li: Original draft preparation. All authors: Suprevision and Editing the original paper.

References

1) Postow MA, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. J Clin Oncol 2015; 33: 1974-1982.
2) Wang DD, Shaver LG, Shi FY, Wei JJ, Qin TZ, Wang SZ, Kong YJ. Comparative efficacy and safety of PD-1/PD-L1 immunotherapies for non-small cell lung cancer: a network meta-analysis. Eur Rev Med Pharmacol Sci 2021; 25: 2866-2884.
3) Sharma P, Siddiqui BA, Anandhan S, Yadav SS, Subudhi SK, Gao J, Goswami S, Allison JP. The Next Decade of Immune Checkpoint Therapy. Cancer Discov 2021; 11: 838-857.
4) Hu HY, Xie XX, Tan ST, Fan X, He J. Extranodal NK/T-cell lymphoma: a case report of renal insufficiency during PD1 inhibitor treatment. Eur Rev Med Pharmacol Sci 2022; 26: 3827-3831.
5) Reynolds K, Thomas M, Dougan M. Diagnosis and Management of Hepatitis in Patients on Checkpoint Blockade. Oncologist 2018; 23: 991-997.
6) Bagchi S, Yuan R, Engleman E. Immune Checkpoint Inhibitors for the Treatment of Cancer: Clinical Impact and Mechanisms of Response and Resistance. Annu Rev Pathol 2021; 16: 223-249.
7) Sasaki A, Kato T, Ujiie H, Cho Y, Sato M, Kaji M. Primary pulmonary lymphoepithelioma-like carcinoma with positive expression of Epstein-Barr virus and PD-L1: A case report. Int J Surg Case Rep 2021; 79: 431-435.
8) Chen B, Zhang Y, Dai S, Zhou P, Luo W, Wang Z, Chen X, Cheng P, Zheng G, Ren J, Yang X, Li W. Molecular characteristics of primary pulmonary lymphoepithelioma-like carcinoma based on inte-

grated genomic analyses. Signal Transduct Targeted Ther 2021; 6: 6.

9) Tang Z, Fang R, Tong G, Liu P, Ou Za, Tang Y. Overcoming resistance to anti-PD-1 immunotherapy in lymphoepithelioma-like carcinoma: A case report and review of the literature. Lung Cancer 2020; 146: 335-340.

10) Xiao Y, He J, Luo S, Dong M, Li W, Liu G, Chen H, Yang X, Huang S. Comparison of Immunotherapy, Chemotherapy, and Chemoimmunotherapy in Advanced Pulmonary Lymphoepithelioma-Like Carcinoma: A Retrospective Study. Front Oncol 2022; 12: 820302.

11) Wu Z, Xian X, Wang K, Cheng D, Li W, Chen B. Immune Checkpoint Blockade Therapy May Be a Feasible Option for Primary Pulmonary Lymphoepithelioma-like Carcinoma. Front Oncol 2021; 11: 626566.

12) Stenzinger A, Kazdal D, Peters S. Strength in numbers: predicting response to checkpoint inhibitors from large clinical datasets. Cell 2021; 184: 571-573.

13) Ma W, Gilligan BM, Yuan J, Li T. Current status and perspectives in translational biomarker research for PD-1/PD-L1 immune checkpoint blockade therapy. J Hematol Oncol 2016; 9: 47.

14) Kanie K, Iguchi G, Bando H, Urai S, Shichi H, Fujita Y, Matsumoto R, Suda K, Yamamoto M, Fukuoka H, Ogawa W, Takahashi Y. Mechanistic insights into immune checkpoint inhibitor-related hypophysitis: a form of paraneoplastic syndrome. Cancer Immunol Immunother 2021; 70: 3669-3677.

15) Lee K, Shaw H, Bataille V, Nathan P. Campylobacteriosis following immunosuppression for immune checkpoint inhibitor-related toxicity. J Immunother Cancer 2020; 8: e000577.

16) Miller E, Abu-Sbeih H, Styskel B, Nogueras Gonzalez G, Blechacz B, Naing A, Chalasani N. Clinical Characteristics and Adverse Impact of Hepatotoxicity due to Immune Checkpoint Inhibitors. Am J Gastroenterol 2020; 115: 251-261.

17) Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, Jordan K. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29: iv264-iv266.

18) Siwicki M, Gort-Freitas NA, Messemaker M, Bill R, Gungabeesoon J, Engblom C, Zilionis R, Garris C, Gerhard GM, Kohl A, Lin Y, Zou AE, Cianciaruso C, Bolli E, Pfirschke C, Lin YJ, Piot C, Mindur JE, Talele N, Kohler RH, Iwamoto Y, Mino-Kenudson M, Pai SI, deVito C, Koessler T, Merkler D, Coukos A, Wicky A, Fraga M, Sempoux C, Jain RK, Dietrich PY, Michielin O, Weissleder R, Klein AM, Pittet MJ. Resident Kupffer cells and neutrophils drive liver toxicity in cancer immunotherapy. Sci Immunol 2021; 6: eabi7083.

19) Riveiro-Barciela M, Barreira-Díaz A, Vidal-González J, Muñoz-Couselo E, Martínez-Valle F, Viladomiu L, Mínguez B, Ortiz-Velez C, Castells L, Esteban R, Buti M. Immune-related hepatitis related to checkpoint inhibitors: Clinical and prognostic factors. Liver Int 2020; 40: 1906-1916.

20) Chascsa DM, Rakela J. Knowns and Unknowns: the Safety and Efficacy of Cancer Immunotherapy in Chronic Liver Disease. Current Hepatology Reports 2018; 17: 1-3.

21) Fu J, Li WZ, McGrath NA, Lai CW, Brar G, Xiang YQ, Xie C. Immune Checkpoint Inhibitor Associated Hepatotoxicity in Primary Liver Cancer Versus Other Cancers: A Systematic Review and Meta-Analysis. Front Oncol 2021; 11: 650292.

22) De Martin E, Michot JM, Papouin B, Champiat S, Mateus C, Lambotte O, Roche B, Antonini TM, Coilly A, Laghouati S, Robert C, Marabelle A, Guettier C, Samuel D. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol 2018; 68: 1181-1190.

23) Ziemer M, Koukoulioti E, Beyer S, Simon JC, Berg T. Managing immune checkpoint-inhibitor-induced severe autoimmune-like hepatitis by liver-directed topical steroids. J Hepatol 2017; 66: 657-659.

24) Goumard C, Perdigao F, Cazejust J, Zalinski S, Soubrane O, Scatton O. Is computed tomography volumetric assessment of the liver reliable in patients with cirrhosis? HPB (Oxford) 2014; 16: 188-194.

25) Kim KW, Ramaiya NH, Krajewski KM, Jagannathan JP, Tirumani SH, Srivastava A, Ibrahim N. Ipilimumab associated hepatitis: imaging and clinicopathologic findings. Invest New Drugs 2013; 31: 1071-1017.

26) Tirumani SH, Ramaiya NH, Keraliya A, Bailey ND, Ott PA, Hodi FS, Nishino M. Radiographic Profiling of Immune-Related Adverse Events in Advanced Melanoma Patients Treated with Ipilimumab. Cancer Immunol Res 2015; 3: 1185-1192.

27) Turunen A, Rautava J, Grénman R, Syrjänen K, Syrjänen S. Epstein-Barr virus (EBV)-encoded small RNAs (EBERs) associated with poor prognosis of head and neck carcinomas. Oncotarget 2017; 8: 27328-27338.

28) Hu J, Zhang X, Yu G, Cai H, Gu J, Hu M, Xiang D, Lian J, Yu L, Jia H, Zhang Y, Yang Y. Epstein-Barr virus infection is associated with a higher Child-Pugh score and may predict poor prognoses for patients with liver cirrhosis. BMC Gastroenterol 2019; 19: 94.

29) Gauci ML, Baroudjian B, Zeboulon C, Pages C, Poté N, Roux O, Bouattour M, Lebbé C. Immune-related hepatitis with immunotherapy: Are corticosteroids always needed? J Hepatol 2018; 69: 548-550.

30) Tan Y, Ye Y, Chen L. Fatal immune-related hepatitis with intrahepatic cholestasis and pneumonia associated with camrelizumab: A case report and literature review. Open Med (Wars) 2021; 16: 553-557.

31) Jennings J, Mandaliya R, Nakshabandi A, Lewis J. Hepatotoxicity induced by immune checkpoint inhibitors: a comprehensive review including current and alternative management strategies. Expert Opin Drug Metab Toxicol 2019; 15: 231-244.