中文題目：Pembrolizumab 在一位晚期肺癌病患引起的免疫性肝炎

英文題目：Pembrolizumab-induced immune-mediated hepatitis in a patient with advanced lung cancer

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Introduction

Pembrolizumab is an immune checkpoint inhibitor that is used in patients with advanced non-small-cell lung cancer (NSCLC). Significantly longer overall survival against platinum-based chemotherapy was reported in those expressing high level of programmed death ligand 1 (PD-L1) [1]. However, excessive immune activation also caused a series of adverse events among different organs. Although most of the adverse events are mild, severe cases do occur and tragedy could happen. The physician should use these immune checkpoint inhibitors cautiously and be aware of the adverse events.

Case Presentation

A 73-year-old female patient presented with poor appetite, easily fatigued, and tea color urine for several days after receiving Pembrolizumab therapy 6 weeks ago. She has a medical history of NSCLC. The clinical stage is T4N1M1b, stage IVA and the immunochemistry staining showed high expression of PD-L1 (> 50%), negative of epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and ROS1 proto-oncogene (ROS1). The Physical examination found markedly icteric sclera. Laboratory data showed aspartate transaminase (AST) 614 U/L, alanine aminotransferase (ALT) 1167 U/L and total bilirubin 16.5 mg/dL (Figure 1). She had no evidence of viral hepatitis. The abdominal sonography found parenchymal liver disease, gallbladder wall thickening with multiple stones. Further laboratory exam found antinuclear antibody (ANA) 1:160, nuclear homogeneous pattern, anti-cell 1 (AC-1), and antimitochondrial antibody (AMA) 1:40. Her liver biopsy showed piecemeal necrosis of hepatocytes with mixed inflammatory cell infiltration is compatible with acute hepatitis (Figure 2A & 2B). The high-dose steroid therapy was prescribed (intravenous methylprednisolone 2 mg/kg/day in first 48 hours, tapered to oral prednisolone 60mg/day from the 3rd day for 2 weeks, then 40mg/day). The patient's liver function recovered well after 2 weeks later.

Discussion

Pembrolizumab is a monoclonal antibody, which blocks the activity of programmed death 1 (PD-1) and allows the T cells to deal with tumor cells. This

immune checkpoint inhibitor is widely used as a first-line treatment for advanced NSCLC patients with a tumor proportion score for PD-L1 of 50% or greater. Pembrolizumab showed significantly longer progression-free and overall survival against platinum-based chemotherapy in those patients [1]. Our patient revealed an obvious regression of tumor size after 1 dose of Pembrolizumab (Figure 3A & B).

The evolution of immunotherapy led cancer therapy into a new era. The wide use of the immune checkpoint inhibitor brought the patient new regimen choices and prolonged lifetime. However, the drug sometimes results in serious adverse events related to excessive immune activation. Those immune-related adverse events (irAE) affect various organs including the skin, gastrointestinal tract, liver, and endocrine organs. In a meta-analysis report, hypothyroidism was reported with the highest incidence during Pembrolizumab therapy [2]. Hepatic toxicity occurs in 1% to 17% of patients, depending on the type of drug and malignancy. Most of them are low-grade toxicity, but grade 3 hepatotoxicity (defined as symptomatic liver dysfunction, with elevated AST or ALT from 5 to 20 times the upper limit of normal (ULN) and/or total bilirubin from 3 to 10 times the ULN) and grade 4 hepatotoxicity (defined as decompensated liver function with elevated AST or ALT over 20 times the ULN and/or total bilirubin over 10 times the ULN) do happen in some cases [3]. The median onset time of hepatitis reported by studies ranges from 6 to 14 weeks after the initiation of PD-1/PD-L1 inhibitor therapy [3][4]. In our case, abnormal liver function up to the level of grade 4 hepatoxicity was first detected after 6 weeks since we initiated Pembrolizumab therapy.

Those patients who present hepatitis as irAE, jaundice, gastrointestinal tract symptoms, poor consciousness and bleeding tendency are the common clinical manufacturers. A laboratory test, abdominal sonography, cross-sectional imaging, and liver biopsy may be helpful for diagnosis. Once the disease was suspected or established, further management should be initiated. According to the American Society of Clinical Oncology (ASCO) guidelines, different therapies from supportive care with close observation to the use of corticosteroids and immunosuppressant, were suggested based on the severity of the disease. Permanently discontinue immune checkpoint inhibitor and administer 2 mg/kg/day methylprednisolone is the first line treatment in grade 4 hepatotoxicity. Immunosuppressant such as mycophenolate mofetil may be considered if no improvement after 3 days of corticosteroid therapy [5]. Fortunately, our patient responded well to corticosteroids and recovered quickly after we started the treatment.

Conclusion

We reported a case of immune-related hepatitis, developed in 6 weeks after Pembrolizumab therapy was initiated. The patient presented with poor appetite, easily fatigued, tea color urine and abnormal liver function. Elevated ANA and AMA led to the suspicion of immune-related hepatitis, which was compatible with later liver biopsy pathology. The patient was treated with corticosteroid therapy according to the ASCO guideline and recovered well. This case reminds us that severe irAE are not common but do occur, which might be fatal while lacking adequate management in time. The physician should always be cautious while using immune checkpoint inhibitors to avoid serious consequences.

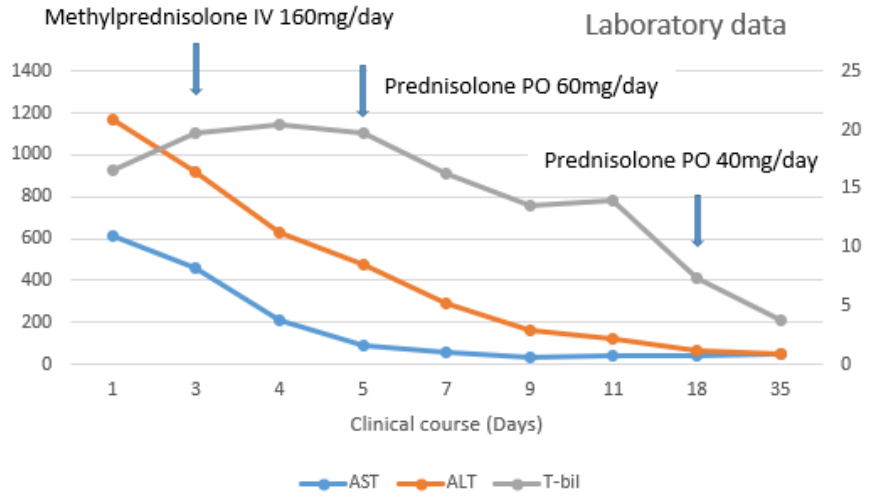

Figure 1. Clinical course and changes of laboratory data. AST, aspartate transaminase; ALT, alanine aminotransferase; T-bil, total bilirubin. (Day18 and Day35 are followed at outpatient clinic.)

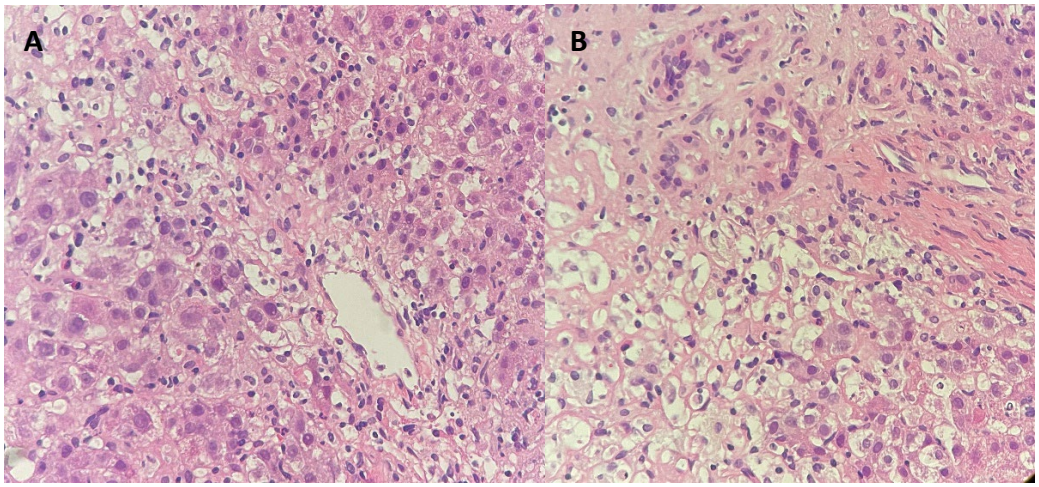

Figure 2. (A)The hepatic plates show foci of mixed lymphocytic and neutrophil infiltration with piecemeal necrosis. (B) The portal areas reveal ductular proliferation and lymphocytic infiltration.

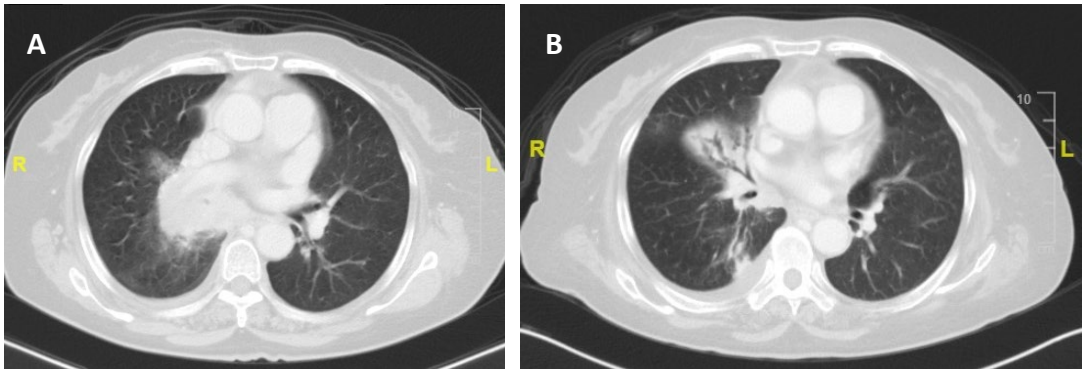

Figure 3. (A) Primary tumor size 56*37mm in right middle lobe. (B) Regression of tumor size to 39*20mm after 1 dose of Pembrolizumab.

References

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