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Case Presentation

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Immunochemotherapy Includes Tislelizumab for Stage IIB Lung Squamous Cell Carcinoma: A Case Report

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Abstract

Background: Primary lung cancer is a malignant tumor with high morbidity and mortality that has been rising in the country. Recently, the rise of immunotherapy has also changed the prognosis and treatment mode of patients with advanced and locally advanced lung cancer. However, the role of immunotherapy in neoadjuvant treatment in patients with non-small cell lung cancer is still worthy of further exploration.

Case description: We report a case of a 63-year-old man with stage IIB squamous non-small cell lung cancer with PD-1/PD-L1 expression levels > 1%. After multidisciplinary consultation, neoadjuvant

treatment with tislelizumab combined with chemotherapy was adopted. During therapy, systemic rash (CTCAE grade 3) and immune hepatitis (CTCAE grade 4) occurred. A dermatologist and gastroenterologist were consulted and the patient improved after treatment. Simultaneously, chest computed tomography (CT) showed a smaller tumor than before and an improved atelectasis of the left upper lung. Due to the immune-related adverse reactions and chest CT results on reexamination post-treatment, tislelizumab was discontinued and surgical treatment was considered. On March 17, 2021, the patient underwent single-port thoracoscopic left upper lobe sleeve resection and mediastinal lymph node dissection in our hospital. The postoperative pathological diagnosis was pathological complete remission, and 4 cycles of adjuvant chemotherapy was given after the operation. No tumor recurrence or metastasis was found so far.

Conclusion: This case further provides evidence for the feasibility and effectiveness of tislelizumab as a neoadjuvant to chemotherapy in the treatment of non-small cell lung cancer. Further randomized controlled and multicenter studies are needed to confirm this.

Keywords: Tislelizumab; Squamousnon-small cell lung cancer; Immunotherapy; Immune-related adverse reactions

Introduction

Lung cancer is the second most common cancer in the world, accounting for about 11.4% of the world's diagnosed cancers and 18.0% of cancer deaths [1]. At present, radical surgical resection is the preferred treatment for patients with stage I, II, and some stage IIIA. For patients who are assessed to be inoperable, combined radical concurrent chemo radiotherapy, immunotherapy, and targeted therapy are often considered [2]. Since the advent of immunotherapy, it has had a huge impact on the treatment of a variety of malignant tumors, providing a great change in treatment prospects of malignant tumors. Immunotherapy is associated with improvements in progression-free survival and overall survival in multiple malignancies [3-5]. Immune Checkpoint Inhibitors (ICIs) are modulators that block the body's antitumor response, including Programmed Death receptor-1 (PD-1), programmed death-ligand 1 (PD-L1), and Cytotoxic T Lymphocyte Antigen 4 (CTLA-4). However, as it causes tumor cell death, immunotherapy can non-specifically activate the immune system and cause damage to normal tissues and organs. Such a series of side effects caused by the use of immune checkpoint inhibitors are collectively referred to as Immune-Related Adverse Reactions (irAE) [6]. These immune-mediated

toxicities can affect almost any organ system, such as the skin, gastrointestinal tract, lung, endocrine, skeletal muscle, kidney, nerve, blood, and cardiovascular system [7]. Here, we report the case of a patient with intermediate-stage squamous non-small cell lung cancer who developed severe systemic rash (CTCAE grade 3) and immune hepatitis (CTCAE grade 4) after receiving 3 cycles of tislelizumab combined with chemotherapy for neoadjuvant treatment. Tislelizumab was finally discontinued after consultation and relevant treatments were received until the rash subsided and the liver function recovered, and a successful radical resection of lung cancer was performed. The postoperative pathology confirmed a successful case of Pathological Complete Remission (PCR).

Case Presentation

A 63-year-old man presented to a local hospital with chief complaint of worsening cough and sputum lasting for more than a month with chest pain and hemoptysis for one day. The patient denied chest tightness, shortness of breath, hoarseness, difficulty swallowing, and other discomforts. Patient history revealed hepatitis B, no history of surgery, no history of allergies, and smoking history for more than 40 years. Physical examination on admission indicated stable vital signs, moderate nutrition (body mass index: 21.2 kg/m^2), no palpable enlarged lymph nodes on both sides of the clavicle, normal and symmetrical bilateral lung respiratory movements, clear sound on percussion, and no obvious dry or wet rales or pleural friction. Auxiliary examination included blood routine, tumor markers, coagulation function, thyroid function, and other examinations, of which all showed no obvious abnormality. Biochemical full set assay showed Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) levels of 25 IU/L and 38 IU/L, respectively. Positron emission tomography/Computed Tomography (CT) showed nodules in the lingual segment of the upper lobe of the left lung, increased metabolism, distal patchy high-density shadows which indicated pulmonary cancer with distal obstructive atelectasis; nodules in the left hilum, increased metabolism indicated lymph node transfer. Chest CT **(Figure 1A)** images presented lingual bronchial nodule in the upper lobe of the left lung, prompting MT removal, accompanied by distal bronchial obstruction and distal atelectasis and consolidation; and small lymph nodes in the left hilum and mediastinum. A diagnosis of squamous cell carcinoma (neoplastic in the opening of the left upper lingual lobe) was confirmed by bronchoscopy biopsy and PD-1/PD-L1 expression level > 1%. Brain magnetic resonance imaging and whole-body skeletal imaging showed no obvious abnormalities. The final diagnosis was stage IIB squamous

non-small cell lung cancer (cT2N1M0) due to the combination of the patient's medical history and related examinations. Multidisciplinary consultation was conducted after admission and after detailed discussions in the departments of thoracic surgery, respiratory medicine, medical oncology, and radiotherapy, the patient was recommended to receive neoadjuvant therapy. The specific regimen was nab-paclitaxel 267mg ivgtt + cisplatin 574mg ivgtt every 3 weeks for 3 cycles, combined with tislelizumab 200mg every 3 weeks for a total of 3 cycles.

The patient underwent the first and second cycles of treatment on September 18, 2020 and October 10, 2020 with no complications. During this period, the liver function test was performed revealing AST and ALT levels of 30 IU/L and 21 IU/L, respectively. Chest CT **(Figure 1B)** showed significantly reduction of the nodules in the upper lobe of the left lung. The patient underwent the third cycle of treatment on October 29, 2020 with no complications. By November 11, 2020, the patient developed a rash **(Figure 2).** On physical examination, pink aggregated macules and papules with pruritus were seen on the chest, back, and limbs, and no rash was found on the face, palms, and soles. Dermatological consultation was requested and the patient was temporarily treated with oral prednisone acetate and bestatine besylate. Simultaneously, liver function test showed ALT and AST levels of 1146.6U/L and 831.2U/L, respectively. Combined with the patient's past history of hepatitis B and related medication history, it was considered that abnormal liver function may be related to the following reasons: 1. immune-related hepatitis; 2. possible reactivation of immune-related hepatitis B virus; 3. possible reaction to nab-paclitaxel and cisplatin injection. Compound glycyrrhizin and polyene phosphatidylcholine was temporarily given for routine liver protection treatment. A review of liver function, hepatitis B virus DNA, hepatitis A antibody, hepatitis C antibody was performed. Liver function test on November 14, 2020 showed ALT levels of 1267.5 IU/L and AST levels of 713.8 IU/L. The patient's hepatitis B virus DNA, hepatitis A antibody, and hepatitis C antibody test showed no obvious abnormality; thus, the possibility of immune-related hepatitis B virus reactivation was ruled out, and routine liver protection and symptomatic treatment did not show significant improvement in liver function abnormality-related indicators. Therefore, considering that the patient had immune-related hepatitis, tislelizumab was discontinued and changed to methylprednisolone to treat immune-related hepatitis, while continuing the original liver-protecting treatment regimen.

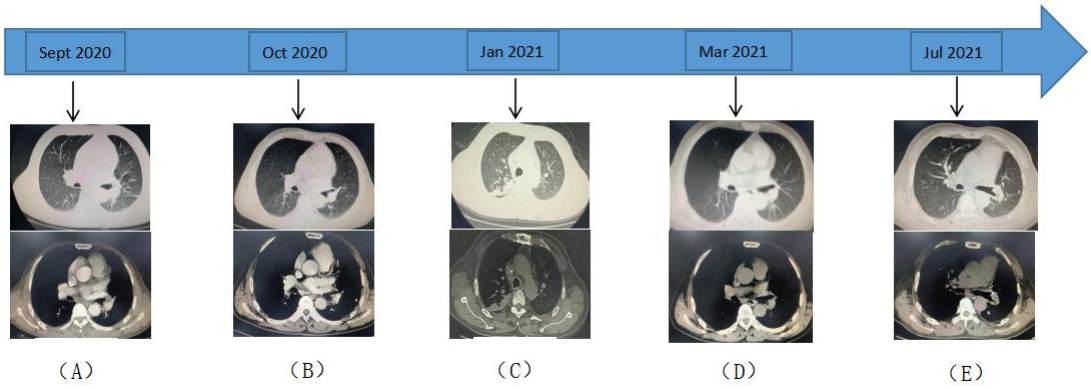

Figure 1: (A) presents the bronchial nodule in the lingual segment of the left upper lung which indicated pulmonary cancer with distal obstructive atelectasis, (B) shows a significantly reduced shadow of the bronchial nodule in the lingual segment of the left upper lung on reexamination after 2 cycles of neoadjuvant therapy, (C) presents the consideration of the presence of new pulmonary infection on reexamination of chest CT, (D) presents the chest CT showing disappearance of the bronchial nodules in the left upper lung lingual segment after 3 cycles of neoadjuvant therapy, (E) the chest CT was repeated three months after the operation and suggested changes in the left upper lung post-operation; no tumor recurrence or metastasis was found.

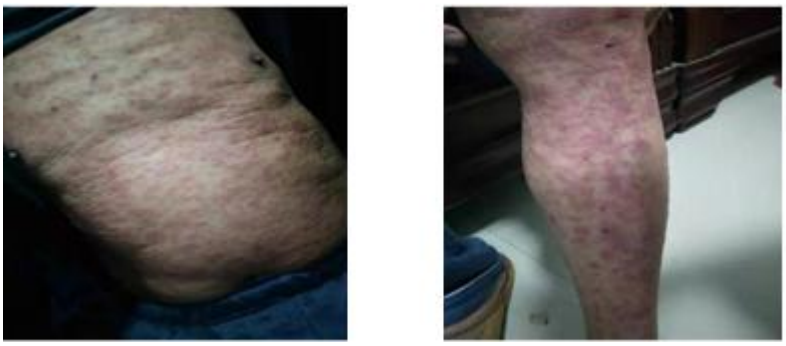

Figure 2: Rash in a patient during treatment with tislelizumab and chemotherapy.

In January 2021, the rash of the patient subsided, and liver function test was normal. After returning to the hospital for preoperative evaluation, chest CT **(Figure 1C)** showed pulmonary infection; thus, the operation was postponed and the patient was sent to the department of respiratory medicine in our hospital. The patient was successively administered with ceftazidime, levofloxacin, imipenem, cilastatin sodium, and other treatments for the infection.

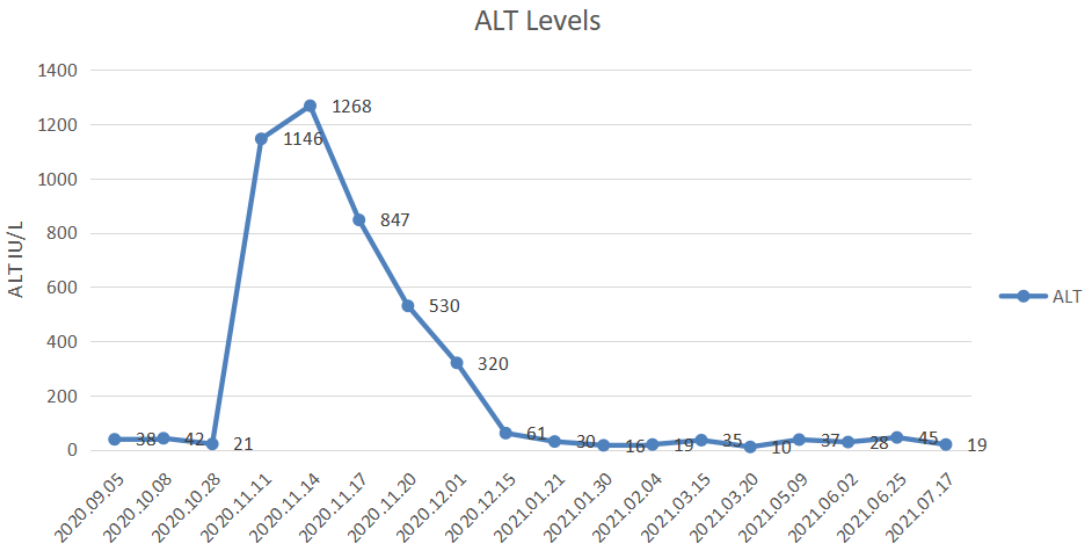

Figure 3: Changes in ALT (alanine aminotransferase) in patients during treatment with tislelizumab combined with chemotherapy.

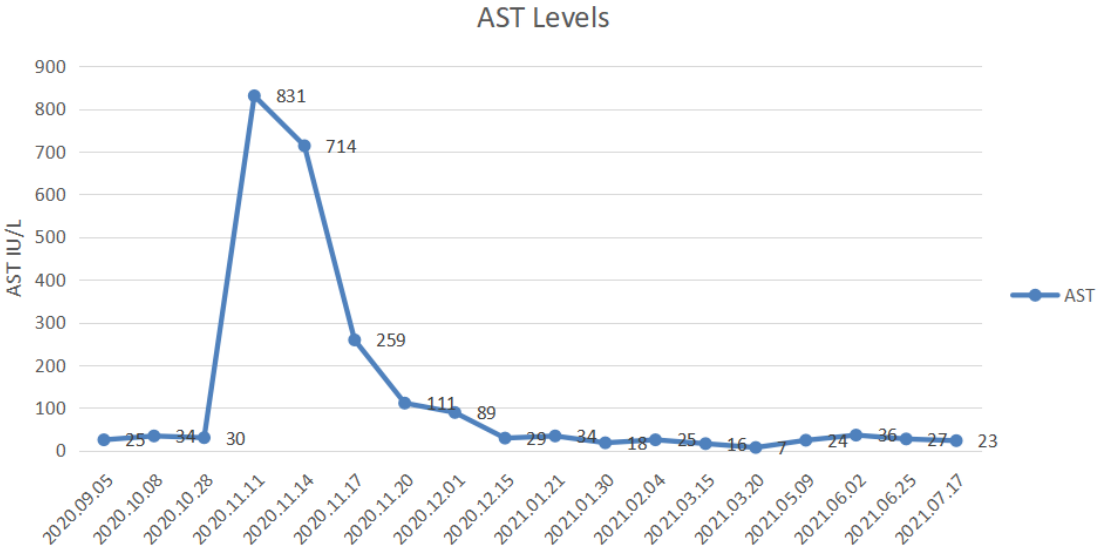

Figure 4: Changes in AST (aspartate aminotransferase) in patients during treatment with tislelizumab in combination with chemotherapy.

In March 2021, the patient's pulmonary infection improved significantly and the patient returned to the hospital for reexamination to rule out contraindication to surgery **(Figure 1D).** On March 17, 2021, the patient successfully underwent single-port thoracoscopic left upper lobe sleeve resection + mediastinal lymph node dissection under general anesthesia. (Because the tumor was close to the bronchus, fiberoptic bronchoscopy was used for biopsy before treatment. To ensure a safe margin,

sleeve resection was selected No residual tumor cells were found, which was consistent with Pathological Complete Remission (PCR). No obvious abnormality was found in the anterior and lateral chest review after operation. Considering that the patient had serious immune-related adverse reactions after preoperative medication, 4 cycles of nab-paclitaxel + cisplatin adjuvant chemotherapy after surgery was planned to be administered. During the period of regular follow-up **(Figure 1E),** no adverse reactions such as rash and abnormal liver function were found. No tumor recurrence or metastasis was found during follow-up.

Discussion

Tislelizumab is a humanized monoclonal antibody against PD-1 with high affinity and binding specificity **[8].** The RATIONALE 307 study showed that in the first-line treatment of patients with advanced squamous NSCLC, tislelizumab combined with chemotherapy significantly prolonged the primary endpoint of PFS compared with chemotherapy alone (median 7.6 months vs. 5.5 months, $p < 0.001$; median 7.6 months vs. 5.5 months, $p < 0.001$), and showed manageable safety and tolerability profiles **[9].** Currently, the NMPA has approved tislelizumab in combination with carboplatin and paclitaxel (or nab-paclitaxel) for the first-line treatment of advanced squamous cell carcinoma of the lung. One study showed that surgery in patients receiving neoadjuvant immunotherapy combined with chemotherapy was safe and feasible, and the final outcome was similar to the patient cohort receiving neoadjuvant platinum-based chemotherapy **[10,11].** Here we report the case of a patient with stage IIB squamous non-small cell lung cancer. The patient's lesion was located in the lingual segment of the left upper lung, involving the lingual bronchus of the left upper lung, distal atelectasis, consolidation, and left hilar lymph node metastasis. After detailed discussions with the department of thoracic surgery, respiratory medicine, oncology, and radiotherapy, preoperative neoadjuvant therapy was planned. The patient received 3 cycles of immunotherapy combined with chemotherapy before surgery. During the process, rash (CTCAE grade 3) and immune hepatitis (CTCAE grade 4) occurred. After consultation and treatment by the dermatology and gastroenterology department, the patient improved. Simultaneously, the chest CT showed reduction of tumor size. Improvement of shrinkage and atelectasis of the left upper lung was observed. Combined with the immune-related adverse reactions and chest CT reexamination results after treatment, we decided to discontinue the drug and consider surgical treatment after discussion. On March 17, 2021, the patient underwent single-port

thoracoscopic left upper lobe sleeve resection + mediastinal lymph node dissection under general anesthesia in our hospital. The postoperative pathology showed that the material was fully collected from the original tumor bed area, and no tumor cells were found under the microscope, which was consistent with Pathological Complete Remission (PCR). After fully evaluating the patient's condition after surgery, we planned to give 4 cycles of adjuvant chemotherapy, and no recurrence or metastasis has been found so far in the follow-up. This case further demonstrates the feasibility and effectiveness of the neoadjuvant regimen of tislelizumab combined with chemotherapy for lung squamous non-small cell carcinoma. With the increasing clinical application of PD-1/PD-L1 inhibitors, the safety profile of tislelizumab has attracted more and more clinical attention. New symptoms should not be ignored whether they occur before or after medication, otherwise it may cause serious consequences. Skin toxicity is one of the most common adverse reactions of immunotherapy, most of which are similar to or aggravated by preexisting skin disease, and may have commonalities with autoimmune-related skin diseases **[12].** Compared with traditional chemotherapy, adverse skin reactions caused by immunotherapy may have delayed onset, ranging from weeks to months or even longer **[13].** Rashes are mainly distributed on the trunk, gradually spreading to the extremities, not usually involving the face. The clinical manifestations are non-specific, and can be light red macules, maculopapular rashes, accompanied by itching, burning sensation, and scaling. It has been reported that the incidence of skin adverse reactions from pembrolizumab is about 14.9%, which is higher than the 12.1% incidence of nivolumab **[14]**. According to statistics, the skin adverse reactions caused by immunotherapy in clinical practice are usually mild and are mainly grades 1-2 according to the CTCAE classification, which does not call for suspension of immunotherapy, and less than 3% progress to grade 3 or 4 **[15].** Notably, the occurrence of certain adverse reactions induced by PD-1/PD-L1 inhibitors seems to predict better treatment response, and a benefit has been reported in both progression-free survival and overall survival in patients with skin immune-related adverse reactions **[16,17].**

Although some studies suggest that the incidence of immune hepatitis due to medication is lower than that of diarrhea and colitis, it is still one of the most common Immune-Related Adverse Reactions (irAEs), usually grade 1-2, and severe to fatal liver failure can still occur in rare cases **[18].** Clinically, it is often manifested as Asymptomatic Elevated Transaminases (AST and ALT), and in rare cases, fever, abdominal pain, and jaundice. The incidence of hepatotoxicity increased significantly with any grade and high-grade hepatotoxicity being 29% and 17%, respectively **[19].** The median time to onset

is usually 5 to 6 weeks after initiation of treatment, but may occur several months later **[19].** In our case, the patient was found to have abnormal liver function after the third cycle of medication. After excluding other related causes, it was considered as immune hepatitis (CTCAE grade 4). For patients with such severe adverse reactions, continuous monitoring during treatment is important. Initially, monitoring of liver function every 1-2 days should be considered. Liver function monitoring (every two weeks to monthly) should continue after hepatotoxicity has resolved markedly or immunotherapy has been completed, as studies have reported recurrence of abnormal liver function in up to one-third of patients **[19,20].**

Of note, the occurrence of certain adverse reactions induced by PD-1/PD-L1 inhibitors seems to predict better treatment response, and it has been reported that in patients with skin immune-related adverse reactions, progression-free survival and overall survival benefit **[21,22].** There is also a multi-center cohort study that the occurrence of multisystem irAEs may be associated with improvements in patient OS and PFS, and this association increases with the type of irAEs occurring. Although these patients may have been treated for longer, the association between the type of irAEs and improved survival was maintained after adjusting for the duration of treatment in these patients. This suggests that such patients may have greater therapeutic benefit and a higher risk of irAEs **[23].**

Conclusion

Our case further provides evidence for the feasibility and effectiveness of neoadjuvant tislelizumab combined with chemotherapy in the treatment of non-small cell lung cancer, although more randomized controlled and multicenter studies are needed to confirm this. Simultaneously, various adverse reactions occur during immunotherapy, compared with traditional chemotherapy, such adverse reactions may delay the onset and last longer. Therefore, when using immunotherapy, we must be vigilant towards new symptoms and signs to achieve early diagnosis and early treatment and to ensure safe drug use while achieving good clinical efficacy.

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