Pulmonary Toxicity by a Cytotoxic Agent, S-1

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Abstract

A 72-year-old man with tongue carcinoma complained of dyspnea on exertion 18 days after starting treatment with S-1. Chest radiograph and CT scan suggested diffuse interstitial lesions with ground glass opacity on both lungs. Bronchoalveolar lavage and transbronchial lung biopsy revealed moderate lymphocyte infiltration with granuloma. Drug lymphocyte stimulation test was positive against tegafur, one of the components of S-1. These findings were consistent with S-1-induced lung injury. Both his symptoms and the radiographic findings were resolved dramatically after high-dose corticosteroid therapy. Clinicians should be aware that S-1 has the potential to cause lung injury when it is included in chemotherapy.

Key words: lung injury, corticosteroid, drug lymphocyte stimulation test (DLST), S-1

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Introduction

Pulmonary toxicity by cytotoxic agents, in theory, falls into three categories according to the mechanisms involved. The first one relates to direct tissue damage by agents, the second one is due to abnormal inflammatory cytokine induction or suppression by the agent’s original function or via the effect of cytotoxicity, and the final one is by allergic reaction to agents (1, 2). Now, a majority of the pulmonary toxicity cases caused by cytotoxic agents are considered a consequence of a combination of the three mechanisms. For example, pulmonary toxicity by bleomycin is initiated by pulmonary vascular endothelial cell damage, followed by imbalance of cytokines and adhesion molecules, resulting in severe damage to the alveolar epithelium and interstitium (3).

S-1 is a recently approved oral anti-neoplastic agent composed of three components, tegafur, 5-C-2, 4-dihydroxypyridine (CDHP), and potassium oxonate (Oxo). Tegafur is a prodrug of 5-FU that has been a key drug for gastrointestinal cancers (4), and the other two components are combined to enhance the cytotoxicity and suppress toxicity. In addition to the clinical relevance of 5-FU, there is an increasing body of evidence to suggest the clinical usefulness of S-1 (5-7).

The major adverse effects of S-1 are hematological and gastrointestinal, but pulmonary toxicity is not well described. Here, we report a case with S-1-induced lung injury, in which the causative component of the drug was identified by lymphocyte stimulation test (DLST), and treatment was performed successfully with corticosteroid therapy.

Case Report

A 72-year-old man with advanced tongue carcinoma (T4N2M0) was scheduled to undergo hemi-glossectomy. S-1 (80 mg/day) was started prior to surgery as induction chemotherapy by an oral and maxillofacial surgeon. Eighteen days after initiation, he experienced dyspnea on exertion and fever (39.0°C), accompanied by severe hypoxemia (PaO₂ of 54.8 torr and PaCO₂ of 24.8 torr). Then he was admitted to the respiratory department of our hospital. He was a current smoker (two packs daily for 50 years) and his past clinical history included mild renal dysfunction from chronic glomerulonephritis, alcoholic liver disease, and gastroesophageal reflux disease. He had been given a proton pump inhibitor (rabeprazole sodium), in addition to S-1.

When he was admitted the respiratory department, physical examination revealed no abnormality except for bilateral fine crackles and pyrexia. Laboratory data included leuko-
Figure 1. (A) HRCT on admission showed diffuse a reticular shadow and ground glass opacity predominantly at subpleural lesions. (B) The lesions were dramatically resolved 7 days after corticosteroid treatment.

Figure 2. Specimen of transbronchial lung biopsy showed moderate lymphocyte infiltration in the pulmonary interstitium with fibro-edematous thickening and mild vasculitis. Granuloma formation (arrow) was also seen (HE, original magnification: × 10).

cyte counts of 3.9×10⁹/L with eosinophilia (12%) and monocytosis (25%), elevated lactate dehydrogenase of 279 U/L, alkaline phosphatase of 495 U/L, IgG of 1,945 mg/dl, IgE of 811 mg/dl, blood urea nitrogen of 27 mg/dl, serum creatinine of 1.45 mg/dl, CRP of 3.4 mg/ml and KL-6 of 750 U/ml. Chest radiograph showed reticular shadows on both lung fields. High-resolution CT scan (HRCT) revealed diffuse interstitial lesions with alveolar septal thickening and ground glass opacity (GGO), predominantly at subpleural lesions without findings of lung volume loss and honeycombing (Fig. 1A).

A pulmonary function test showed a marked decrease in diffusing capacity of carbon monoxide (32.5% of predicted). Microbiological examination was unremarkable including negative antigen of Cytomegalovirus, Legionella pneumophila, negative PCR data for Mycobacterium tuberculosis, Pneumocystis jiroveci, and negative antibodies to Mycoplasma pneumoniae and Chlamydia pneumoniae. Bronchoalveolar lavage (BAL) from the right middle lobe showed moderately increased cell counts (3.0 × 10⁵/ml) with lymphocyte predominance (alveolar macrophages 17%, lymphocytes 79%, eosinophils 2%, and neutrophils 2%) and a normal T lymphocyte ratio of CD4/CD8 as 2.48. Transbronchial lung biopsy (TBLB) from the anterior segment of the right lower lobe demonstrated moderate lymphocyte infiltration with granulomas (Fig. 2). DLST was employed for the possible drugs that he was given. The three components of S-1 were examined independently. The stimulation index (SI) cut-off was set at 200%, and each drug was examined at multiple concentrations. At higher concentrations, S-1 and tegafur showed an apparently positive response (the maximum SI of 460 and 619, respectively), whereas for rabeprazole sodium, CDHP yielded negative results. DLST for Oxo showed a positive result with mild elevation of SI (246%) only at one dilution point (Fig. 3). Taken together, a diagnosis of drug-induced lung injury was established. By the time of the diagnosis, S-1 and rabeprazole had been discontinued, although hypoxia and fever were still present.

High-dose corticosteroid (500 mg of methylprednisolone) was initiated intravenously for three consecutive days followed by oral prednisone (1 mg/kg/day). Seven days after treatment, both his symptoms and radiographic findings were dramatically resolved (Fig. 1B). Also, alveolar-arterial oxygen gradient (A-aDO₂) was significantly decreased from 64.2 to 40.8 torr, and predicted diffusing capacity was increased from 32.5 to 60.3% after treatment (Fig. 4).

Discussion

Most antineoplastic drugs have the potential to induce pulmonary toxicity, involving lung parenchyma, airways, pleura, and pulmonary circulation (8). The mainstay of treatment of drug-induced pneumonia is to identify and remove the causative agent as soon as possible. However, diagnosis is often difficult due to the patient’s confounding factors, i.e. pulmonary co-morbidities and other modalities such as concomitant chemotherapy and radiation therapy (9).
Figure 3. Results of DLST with drugs administered to the patient. The three components of S-1 were also examined separately. Each agent, diversely diluted from 50 ~50^6 fold of the original concentration (indicated in the figure), was added to culture medium containing the patient’s peripheral lymphocytes. Note that the tests with tegafur and S-1 provided positive results at multiple dilution points. The figure also indicates the level of negative control and threshold for judging as positive.

Figure 4. Clinical course. Interstitial pneumonia induced by S-1 dramatically responded to corticosteroid therapy.

Interstitial lung disease is the most common form of drug-induced lung injury. Based on TBLB findings, the present case was proven to have interstitial pneumonia, which indeed responded to corticosteroid treatment. DLST was also helpful for establishing the diagnosis. Although the result of DLST with Oxo was positive with mild elevation of SI at one dilution point, this was not reproducible with other dilution points. As the test was performed with multiple dilution points for each agent, and the three components of S-1 were examined independently, the pneumonitis of the present patient was considered to be drug-induced, most likely by tegafur. Kurakawa et al reported the first case of S-1-associated lung injury diagnosed by DLST, without specifying a causative component (10).

The interpretation of DLST for antineoplastic drug requires a certain caution. Some anti-metabolites directly affect the 3H-thymidine uptake of lymphocytes by inhibiting DNA de novo synthesis, which could result in a false negative response. However, tegafur is able to elicit enhanced T-cell proliferation even in non-sensitized individuals. In fact, 1 out of 10, and 4 out of 20 healthy volunteers showed positive response against UFT (11), and S-1 (12), respectively, when the SI cut-off was set at 200%. It would be important to note, however, that the SI in these healthy volunteers was not so very high, except for one subject with SI of 460% against S-1 (12), that is, it ranged from 124 to 204% against UFT, and from 90 to 247% against S-1. This means that attention should be paid to the evaluation of DLST data with anti-metabolites, and diagnosis should be made in combination with other circumstantial evidence. The present case was most likely affected with hypersensitivity to tegafur, with other clinical findings including eosinophilia and an elevated IgE level.

Pulmonary toxicity of S-1 has rarely been reported. Other cytotoxic agents, 5-FU (active form of S-1) and UFT, which also includes tegafur, however, have been reported to cause mortality by lung injury (13, 14). As the use of S-1 becomes more common, the incidence of S-1 related pulmonary toxicity may also increase. All clinicians should be aware that S-1 has the potential to cause lung injury.

References


