CASE REPORT

S-1-induced lung injury combined with pneumocystis pneumonia

Shuichi Yano

National Hospital Organization
Matsue Medical Center,
Matsue, Japan

Correspondence to
Dr Shuichi Yano,
yano@matsue.hosp.go.jp

SUMMARY

Pulmonary injuries due to S-1 have been reported, and these reports have shown an increase in lung cancer following the increased usage of S-1 in treating lung cancer. We report the first case of lung injury due to S-1 in combination with pneumocystis pneumonia (PCP), because the radiological findings and clinical courses were compatible with S-1-induced lung injury combined with PCP. We should consider that S-1 might induce lung injuries which might occur with PCP, especially with a history of drug-induced or radiation-induced lung injuries.

BACKGROUND

S-1 is an oral antineoplastic agent that consists of three components (tegafur (5-C-2), 4-dihydropyridine and potassium oxonate). Tegafur is a prodrug of 5-FU, which is a key drug in the treatment of gastrointestinal cancers. S-1 has been approved for the treatment of the following cancers in Japan: gastric, head and neck, colorectal, nonsmall cell lung, breast, pancreatic, and biliary tract. Several reports have shown pneumonitis associated with S-1, as with other anticancer drugs.^{1–3} The adverse effects of medications on the lung are an increasing problem, given the rapidly growing number of drugs used for therapeutic and illicit purposes. In addition to a wide variety of clinical manifestations, there is a broad spectrum of histological patterns of pulmonary reactions to drugs.^{4–6}

CASE PRESENTATION

A 70-year-old man with low-grade fever and a sudden onset of dyspnoea for 5 days presented to our hospital on 30 July 2012. He had been treated for stage IIIB left upper lung cancer since June 2009. Carboplatin (CBDCA) with paclitaxel, and cisplatin (CDDP) with vinorelbine or irinotecan were administered as first-line to third-line platinum-based chemotherapies for 23 months. Erlotinib was started on 19 April 2011, but 3 months later the patient complained of a sudden onset of exertional dyspnoea and was diagnosed with erlotinib-induced lung injury. After an improvement with prednisolone, CBDCA, bevacizumab and pemetrexed sodium hydrate (PEM) were administered for four cycles and PEM was continued as maintenance therapy. On 19 April 2012, the patient was admitted with complaints of refractory cough and dyspnoea. A bronchoscopic examination showed complete obstruction of the left lower bronchus and a pinhole obstruction of the left upper bronchus. The patient was then

treated with palliative radiotherapy (50 Gy) to the left hilar mass. On 26 June 2012, S-1 (120 mg/day) was begun as sixth-line chemotherapy.

INVESTIGATIONS

On the present admission, the white blood cell count was 9200/mm³, with 85% neutrophils, 8% lymphocytes, 6% monocytes and 1% eosinophils. The serum C-reactive protein (CRP) was increased to 10.0 mg/dl. The aspartate aminotransferase level was slightly increased (39 IU/l). Renal functions were normal and the serum fasting glucose level was elevated (185 mg/dl). The serum carcinoembryonic antigen (CEA) and KL-6 levels (Eisai co, Ltd, Tokyo, Japan, normal, lower 500 U/ml) were elevated at 104.7 ng/ml and 1437 U/ml, respectively. The serum β -D glucan level (Wako Pure Chemical Industries Ltd, Osaka, Japan) was 13.5 pg/ml. *Aspergillus* and cytomegalovirus antigen testing was negative. Urine antigen testing (Binax Now; Alere Medical co, Ltd, USA) for *Streptococcus pneumoniae* and *Legionella pneumophila* was negative. A plain chest radiograph demonstrated bilateral lung infiltration, especially in the lower lobe (figure 1A). Chest CT showed bilateral lung ground glass opacities (GGOs), which were sharply demarcated from the adjacent normal lung, and diffuse infiltration with air bronchograms (figure 1B). The left S⁶ primary tumour was enlarged with cavity formation and showed multiple nodular metastatic lesions in the bilateral lung fields (figure 1C). The lymphocyte stimulating test (LST) for S-1 was reported to be positive (maximum stimulation index 4.7). *Pneumocystis jirovecii* sputum PCR (PCJ; Mitsubishi Chemical Medience Co, Tokyo, Japan) was positive and the β -D glucan increased to 19.3 pg/ml after 10 hospital days.

DIFFERENTIAL DIAGNOSIS

In the current case, S-1 was administered for 1 month, after which the patient complained of a sudden onset of dyspnoea and fever. A chest CT on admission showed bilateral lung GGOs, which progressed after the fifth hospital day and were thought to be complicated with pneumocystis pneumonia (PCP). Nodular infiltration with air bronchograms among the CT findings was suspected to be due to drug-induced lung injury. We diagnosed that the radiological findings were compatible with S-1-induced lung injury combined with PCP. As the serum LST was positive for S-1, we diagnosed a drug-induced lung injury. Kawabata *et al.* reported that LST could show a false-positive response through an intracellular function that accelerates the incorporation of thymidine in the

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Figure 1 (A) Chest radiograph on admission; (B) chest CT on admission; (C) chest CT on admission showed the left S⁶ primary tumour with cavity formation that enlarged and showed multiple nodular metastatic lesions in the bilateral lung fields; (D) chest radiograph on 4 July; (E) chest radiograph on 10 September.

lymphocytes by the salvage pathway after inhibition of DNA de novo synthesis caused by 5-FU derivative anticancer, including S-1.⁷ However, the patient was in good performance status when S-1 was started, and he suddenly complained of dyspnoea after it was administered for about 1 month. Since PCR for PCJ was positive and the β -D glucan increased to 19.3 pg/ml after 10 hospital days, we thought that he suffered from S-1 lung injury at first, which was later complicated with PCP.

TREATMENT

S-1 was stopped immediately; 5 l O₂/min was administrated via face mask, and methylprednisolone (250 mg/day) and cefepime dihydrochloride (2 g/day) were initiated on 30 July. After 5 days of therapy, the CRP value decreased to 1.96 mg/dl. With progressing lung infiltration (figure 1D), the antibiotics were changed to ciprofloxacin (CPFX; 600 mg/day) and trimethoprim-sulfamethoxazole (TMP/SMX; 9 g). Since PCJ sputum PCR was positive and the β -D glucan increased to 19.3 pg/ml after 10 hospital days, CPFX therapy was stopped. LST for S-1 was reported to be positive. Therefore, we diagnosed PCP after S-1-induced pneumonitis. Methylprednisolone therapy was decreased to prednisolone at

30 mg/day after an improvement in hypoxaemia on 5 August. We gradually decreased the prednisolone dosage. The sputum culture was negative for pathogens, and the serum β -D glucan level decreased. Since the patient's condition was improving, we continued TMP/SMX therapy.

OUTCOME AND FOLLOW-UP

On 10 September, the chest radiograph showed an improvement in the bilateral lung infiltration (figure 1E); however, the lung metastatic nodules were enlarged in size.

DISCUSSION

Drugs can cause lung injuries via multiple mechanisms, including: the oxidant/antioxidant system, the immune system, matrix repair, proteases/antiproteases and interference with lipid metabolism and the central nervous system (CNS). Drug toxicity can result from direct or indirect injuries to the lung. Direct toxicity can occur through toxic or idiosyncratic mechanisms. Indirect effects on the lungs may result from suppressive effects on the CNS, immune system or haematopoiesis.⁴ In the current case, S-1 was administered for 1 month, after which the patient

complained of a sudden onset of dyspnoea and fever. Tasaka *et al*⁸ reported that no AIDS patients demonstrated consolidation, whereas half of the patients with malignancies had consolidation along with GGOs. In the current case, a chest CT on admission showed bilateral lung GGOs, which progressed after the fifth hospital day and were thought to be complicated with PCP. Nodular infiltration with air bronchograms among the CT findings was suspected to be due to drug-induced lung injury. We diagnosed that the radiological findings were compatible with S-1-induced lung injury combined with PCP. As the serum LST was positive for S-1, we diagnosed a drug-induced lung injury. Kawabata *et al* reported that LST could show a false-positive response through an intracellular function that accelerates the incorporation of thymidine in the lymphocytes by the salvage pathway after inhibition of DNA *de novo* synthesis caused by 5-FU derivative anticancer, including S-1.⁷ However, the patient was in good performance status when S-1 was started, and he suddenly complained of dyspnoea after it was administered for about 1 month. We thought that he suffered from S-1 lung injury than PCP at first. The serum β -D level gradually increased after the 10th hospital day; thus, we diagnosed that S-1-induced pneumonitis preceded PCP. The cut-off levels for β -D glucan in PCP have been reported to be 31.1 pg/ml based on an receiver operating characteristics curve.⁹ The sensitivity and specificity of β -D glucan were 92.3% and 86.1%, respectively. Although the β -D glucan level was lower in this case than the reported data, the sputum PCR for PCP was also positive and the values of β -D glucan increased following deterioration of the disease. The β -D glucan value increased consistent with worsening of hypoxaemia and radiological findings, and decreased with TMP/SMX treatment. However, we could not completely determine the order of S-1-induced lung injury or PCP. The diagnosis is often difficult due to patient confounding factors, that is, pulmonary comorbidities and modalities such as concomitant chemotherapy and radiotherapy.¹⁰ Before administration of S-1, the patient underwent left hilar radiotherapy. After radiotherapy, radiation pneumonitis occurred and steroids were administered. When S-1 was administered, the symptoms of radiation pneumonitis disappeared with slight residual right lung opacity. However, the residual lung lesion might have affected the S-1-induced lung injury. The patient had a history of erlotinib

lung injury and might have had a predisposition to drug-induced lung injuries.

We should consider that S-1 might induce lung injuries which might occur with PCP, especially with a history of drug-induced or radiation-induced lung injuries.

Learning point

We should consider that S-1 might induce lung injuries which might occur with pneumocystis pneumonia (especially with a history of drug-induced or radiation-induced lung injuries).

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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