

A case of acute and severe thrombocytopenia due to readministration of rifampicin

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Abstract A 49-year-old-woman was diagnosed with tuberculosis of the left humerus. She had received treatment, including rifampicin, for tuberculosis 17 years previously. Treatment was begun with isoniazid, rifampicin, ethambutol, and pyrazinamide, but these were discontinued because of mild neutropenia and thrombocytopenia 2 weeks posttreatment. Rifampicin and ethambutol were readministered after a 4-day interruption; however, generalized purpura appeared several hours later. By the next day, her platelet count was reduced from 160×10^3 to $3 \times 10^3/\mu\text{l}$. The patient improved rapidly after platelet transfusion and steroid treatment. Readministration of drugs other than rifampicin did not induce thrombocytopenia; therefore, thrombocytopenia was likely due to rifampicin.

Keywords Tuberculosis · Thrombocytopenia · Rifampicin · Allergy · Steroid

Introduction

Antitubercular drugs are associated with a variety of adverse effects. Rifampicin (RFP) is a key drug in the treatment of tuberculosis [1]. However, it is well known that RFP sometimes induces allergic reactions, especially upon readministration [2]. On the other hand, several drugs, including RFP, rarely induce thrombocytopenia through an immune mechanism [3]. Here we reported a case of acute and severe thrombocytopenia occurring within 1 day after a second readministration of RFP.

Case report

A 49-year-old-woman suffering from left shoulder pain was admitted to our hospital. Seventeen years previously, she had received isoniazid (INH), rifampicin (RFP), and ethambutol (EB) for 1 year to treat pulmonary tuberculosis. The medications were administered without interruption and induced with no adverse reactions, including hematological disorders. There were no abnormal findings on her physical examination. Her chest roentgenogram showed no abnormal shadows in the bilateral lungs (Fig. 1), and *Mycobacterium tuberculosis* was not detected in her sputum. On admission, her white blood cell (WBC) count was $3,530/\mu\text{l}$ and her platelet (PLT) count was $202 \times 10^3/\mu\text{l}$.

Magnetic resonance imaging (MRI) demonstrated an osteolytic lesion of the left humeral head, which led to the findings consistent with an early phase of tuberculous osteomyelitis (Fig. 1). Several diseases were considered in the differential diagnosis of the lesion; for example, bacterial osteomyelitis, sarcoidosis, or metastases [4]. However, no other abnormalities were found on her physical findings

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Fig. 1 Chest X-ray and magnetic resonance imaging (MRI) of the left humerus on admission. Chest X-ray demonstrated no abnormal shadows (*left*). Axial short-tau inversion recovery (STIR)/T2-weighted MRI indicated a tuberculous lesion (*right*). The high signal intensity in the lesser tuberosity of the humerus extends over the anterior part of the humeral head; however, there was no abscess around the lesion and no excessive joint effusion. This image demonstrates findings consistent with an early phase of tuberculous osteomyelitis without articular tuberculosis

and examinations, and bone biopsy might induce impairment of motor function in this case. Therefore, she was clinically diagnosed as having tuberculous osteomyelitis and she agreed with the diagnostic therapy for tuberculosis. Antitubercular treatment with 300 mg INH, 450 mg RFP, 750 mg EB, and 1,000 mg pyrazinamide (PZA) was initiated. Pyridoxal phosphate hydrate and rebamipide were also administered at the same time. However, her WBC count decreased to 2,680/ μL and PLT count to $128 \times 10^3/\mu\text{L}$ 2 weeks later. The thrombocytopenia and mild neutropenia were thought to be effects of antitubercular drugs, the myelosuppression due to INH in particular, so all drugs were discontinued. Five days later, her WBC count recovered to 3,230/ μL and the PLT to $161 \times 10^3/\mu\text{L}$. Only RFP and EB were then readministered, whereupon generalized purpura and bleeding from the nose and gums appeared several hours later. The PLT count decreased to $3 \times 10^3/\mu\text{L}$ the next day. RFP and EB were then discontinued, and the patient received a PLT transfusion and steroid pulse therapy with 1 g methylprednisolone for 3 days. A rapid improvement in symptoms was evident within a few days, and her PLT count recovered to $145 \times 10^3/\mu\text{L}$ by day 5 (Fig. 2). RFP showed a positive reaction in the drug-induced lymphocyte-stimulation test (DLST) (RFP = 356% and EB = 186% vs. normal range of <180%).

After 1 week, treatment with levofloxacin was begun, and subsequently, INH (200 mg), PZA, and EB were readministered in that order. Although antitubercular therapy with these four drugs was continued for 2 years, only transient, mild neutropenia was noted, and thrombocytopenia did not relapse. The PLT count during that time remained in the range of 150×10^3 to $200 \times 10^3/\mu\text{L}$, and the left humeral lesion gradually improved.

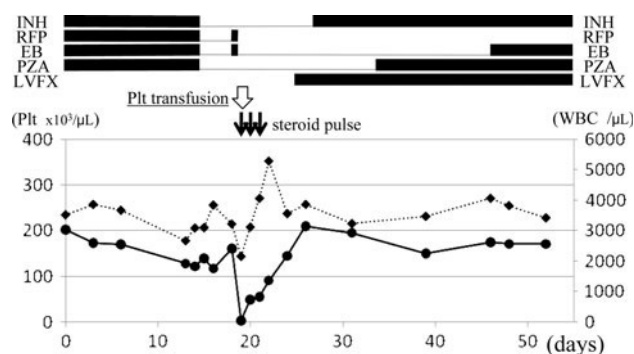


Fig. 2 The course of the platelet (PLT) and white blood cell (WBC) counts during therapy for tuberculosis. PLT count was reduced from 161×10^3 to $3 \times 10^3/\mu\text{L}$ after rifampicin and ethambutol were readministered. The patient received a PLT transfusion and steroid pulse therapy with methylprednisolone for 3 days after RFP and EB were stopped, which resulted in rapid improvement of PLT count to $145 \times 10^3/\mu\text{L}$ 5 days later (*circles* PLT count, *squares* WBC count. INH isoniazid, RFP rifampicin, EB ethambutol, PZA pyrazinamide, LVFX levofloxacin)

Discussion

Antitubercular drugs often induce various adverse effects, such as gastrointestinal disorders, liver dysfunction, and allergic reactions [1]. RFP has been reported to induce allergic responses, especially when readministered after a treatment interruption [2]. Hematological disorders due to various causes have also been noted during antitubercular therapy. In the case reported here, the antitubercular drugs INH, RFP, EB, and PZA administered for 2 weeks were associated with a gradual decrease in WBC and PLT counts. We initially suspected that the cause of these adverse events was mild myelosuppression due to one of the antitubercular drugs. INH seemed to be the most likely culprit because it is known to sometimes induce neutropenia as a result of cytotoxic damage to the bone marrow [5]. However, generalized purpura and bleeding from the nose and gums appeared several hours after readministration of RFP and EB, suggesting that one of these agents may have been responsible for the hematological side effects seen in our patient. One month after discontinuation, EB was readministered with the patient's consent, and there were no obvious adverse effects. Through the process of elimination, RFP was identified as the causative agent for the severe thrombocytopenia observed in our patient and, therefore, a rechallenge test with RFP was not performed. Mild thrombocytopenia, seen during administration of the four drugs, was due to RFP rather than INH, as thrombocytopenia did not relapse after INH, EB, and PZA were readministered, whereas administration of RFP with EB resulted in severe thrombocytopenia.

There have been rare case reports of thrombocytopenia due to an allergic response to RFP [6, 7]. In most of these

cases, thrombocytopenia occurred within 1 month after RFP administration. Conversely, thrombocytopenia has also been reported within several days of treatment with RFP, particularly in cases in which RFP was being readministered. Pau and Fisher reported a case in which thrombocytopenia was noted after only 4 days of RFP treatment and without prior exposure to RFP [8]. Lee and Lee [7] reported that readministration of RFP within a 2-month interval after initial exposure induced generalized purpura after 1 week; however, a second readministration of RFP induced acute thrombocytopenia with a decrease in PLT from 711×10^3 to $8 \times 10^3/\mu\text{l}$ within 5 h. These results are consistent with those of our study; i.e., the preceding treatment with RFP caused mild thrombocytopenia within a few several days, whereas readministration of RFP rapidly resulted in severe thrombocytopenia. Few cases of RFP-induced acute thrombocytopenia with PLT counts $<3,000/\mu\text{l}$ have been reported. It is important to confirm the histories of RFP administration before commencing RFP treatment for patients with tuberculosis [8].

The mechanism for acute thrombocytopenia due to RFP appears to be clear. The antiplatelet antibodies of a patient with RFP-induced thrombocytopenia form an antigenic complex with RFP that interacts with blood-cell membrane proteins [9, 10]. Two pivotal studies indicate that antibodies interact drug-dependently with the platelet glycoprotein Ib-IX complex [11, 12]. Several drugs, such as quinine and quinidine and ranitidine are also known to induce drug-dependent thrombocytopenia by such a mechanism [13, 14].

Some investigators concluded that interruption of RFP treatment alone is the measure needed to counter RFP-induced thrombocytopenia because PLT counts improve soon afterwards [7]. It is possible that discontinuation of RFP is sufficient if the symptoms are not severe. However, our patient required platelet transfusion and steroid pulse therapy to control severe bleeding. One report described a case of severe RFP-induced thrombocytopenia, which led to acute subdural hemorrhage [15]. Platelet transfusion and steroid treatment should therefore be considered in cases with obvious symptoms of bleeding.

We reported a case of acute and severe thrombocytopenia due to readministration of RFP. This case illustrates that immune thrombocytopenia can occur as a rare but serious complication of RFP treatment.

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