

[ CASE REPORT ]

## Isoniazid-induced Immune Thrombocytopenia

Gaku Kuwabara<sup>1,2</sup>, Kumiyo Tazoe<sup>3</sup>, Waki Imoto<sup>1,2</sup>, Kazushi Yamairi<sup>1</sup>, Wataru Shibata<sup>1</sup>, Kazuhiro Oshima<sup>1</sup>, Koichi Yamada<sup>1</sup>, Yasuhiro Takagi<sup>4</sup>, Satoshi Shiraishi<sup>4</sup>, Masayuki Hino<sup>3</sup>, Tomoya Kawaguchi<sup>2</sup> and Hiroshi Kakeya<sup>1</sup>

### Abstract:

Drug-induced thrombocytopenia occurs through immune-mediated platelet destruction, and its management is challenging during tuberculosis treatment. Although rifampicin is the most common drug causing thrombocytopenia, isoniazid can also cause thrombocytopenia. We herein report a 75-year-old man who developed thrombocytopenia during tuberculosis treatment. Platelet-associated immunoglobulin G and a drug-induced lymphocyte stimulation test for isoniazid were positive; no other causes of thrombocytopenia were identified. The patient was diagnosed with isoniazid-induced immune thrombocytopenia, and the platelet count normalized after isoniazid discontinuation. We describe the immunological mechanism of thrombocytopenia due to isoniazid, an uncommon cause of thrombocytopenia that physicians should be aware exists.

**Key words:** drug-induced immune thrombocytopenia, isoniazid, tuberculosis

(Intern Med 60: 3639-3643, 2021)

(DOI: 10.2169/internalmedicine.6520-20)

### Introduction

Tuberculosis is a chronic granulomatous infection that has caused epidemiological problems for over a century and requires long-term antimicrobial treatment, which can have various side effects. Skin rashes, hepatotoxicity and digestive symptoms, such as diarrhea and loss of appetite, are among the common side effects of anti-tuberculosis drugs. Although tuberculosis treatment is challenging because of these side effects, serious side effects are rare.

Thrombocytopenia is an uncommon but possible side effect caused by anti-tuberculosis drugs that can be life-threatening. Rifampicin (RFP) is the most common causative drug among anti-tuberculosis drugs (1-5). However, studies have reported only a few cases of isoniazid (INH)-induced thrombocytopenia (5-10).

We herein report a case of severe drug-induced immune thrombocytopenia caused by INH.

### Case Report

We herein report a 75-year-old Japanese man with a medical history of spondylitis at 72 years and no medical history of tuberculosis. He was diagnosed with tuberculosis and tuberculous spondylitis. Chest radiography showed bilateral nodular shadow and an infiltrative shadow of the left lung (Fig. 1), and treatment was initiated with RFP (600 mg/day), INH (300 mg/day), ethambutol (EB, 500 mg/day) and pyrazinamide (PZA, 1.2 g/day) at another hospital. Posterior lumbar spinal fusion was performed subsequently.

As hepatic toxicity occurred after 1 month [aspartate transaminase (AST), 164 U/L; alanine transaminase (ALT), 186 U/L], drugs were discontinued for 4 weeks until hepatotoxicity improved. During this period, the platelet count dropped to  $9.0 \times 10^4 / \mu\text{L}$  at 11 days after drug discontinuation and thereafter increased to  $13.6 \times 10^4 / \mu\text{L}$ . Although the patient was desensitized with INH and RFP after the hepatic function improved (INH and RFP doses started at 50 and 75 mg/day, respectively, and increased 2-fold every 3

<sup>1</sup>Department of Infection Control Science, Graduate School of Medicine, Osaka City University, Japan, <sup>2</sup>Department of Respiratory Medicine, Graduate School of Medicine, Osaka City University, Japan, <sup>3</sup>Department of Hematology, Graduate School of Medicine, Osaka City University, Japan and <sup>4</sup>Department of Respiratory Medicine, Osaka City Juso Hospital, Japan

Received: October 15, 2020; Accepted: April 13, 2021; Advance Publication by J-STAGE: May 29, 2021

Correspondence to Dr. Hiroshi Kakeya, kakeya@med.osaka-cu.ac.jp



## Chest radiography

**Figure 1.** Chest radiography at the diagnosis showed bilateral nodular shadow and infiltrative shadow of the left lung.

days, finally reaching 300 and 600 mg/day, respectively), hepatotoxicity occurred again (AST, 94 U/L; ALT, 76 U/L). Therefore, RFP was discontinued, and treatment with INH and EB was continued. The patient was transferred to our hospital 3 months after the initiation of the treatment (10 days after discontinuation of RFP) because continuing the treatment at that hospital was deemed difficult.

Laboratory investigations on admission showed a low platelet count of  $1.5 \times 10^4/\mu\text{L}$  (Table 1). Therefore, platelet transfusion of 10 and 20 units was done on days 1 and 2, respectively. Red blood cell transfusion of two units was also performed for anemia on day one. According to laboratory investigations, secondary anemia was diagnosed because of tuberculosis. The decrease in the platelet count was associated with the administration of INH, after reviewing the course and medications (Fig. 2A). Therefore, INH was discontinued on the third day, and levofloxacin (500 mg/day) and streptomycin (0.3 g/day) were added. No bacteria were detected from cultures of blood, sputum or urine, excluding the *Mycobacterium tuberculosis* detected from sputum culture. An elevated immature platelet fraction of 24.7% (normal range, 2-10%) implied accelerated platelet destruction. Platelet-associated immunoglobulin G (PA-IgG) was positive, and INH was positive using the drug-induced lymphocyte stimulation test (DLST), while RFP was negative. No rash or bleeding symptoms were noted.

Bone marrow aspiration was performed to exclude hematological malignancies and bone marrow tuberculosis, and no specific findings, including malignant and granulomatous

findings, were revealed by the histopathological analysis (Fig. 3). Although the platelet count decreased again after platelet transfusion, which implied the continuation of the antibody-mediated destruction of platelets, the decrease stopped five days after INH was discontinued, and the platelet count gradually improved (Fig. 2B). Based on these findings and the interval between drug discontinuation and the cessation of the decrease in the platelet count, INH-induced immune thrombocytopenia was suggested. Rifabutin (RBT) was added to the RFP regimen as an alternative drug, as RFP was considered a causative agent of liver toxicity. Thrombocytopenia did not occur after the addition of RBT. Although a sputum smear for acid-fast bacilli remained positive, the general condition of the patient was stable, and chest radiography showed no significant changes after admission to our hospital. Subsequently, the patient was transferred to another hospital eight weeks after his transfer to our hospital for the continuation of treatment.

## Discussion

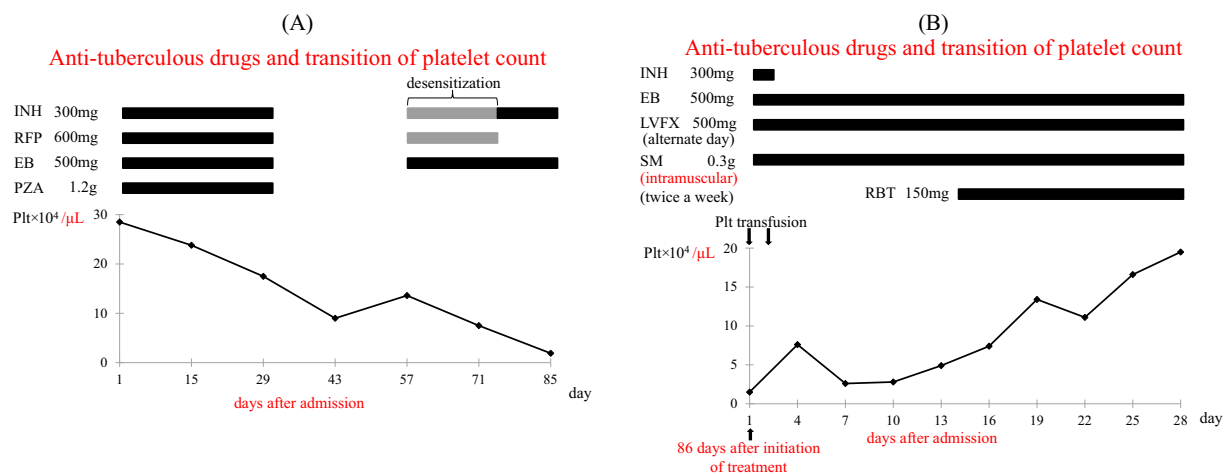
Although anti-tuberculosis drugs can cause various side effects, it is rare to experience severe thrombocytopenia that necessitates drug discontinuation. Among anti-tuberculosis drugs, RFP is most commonly associated with thrombocytopenia (1-4, 10), whereas INH-induced thrombocytopenia is relatively uncommon (5-10). In this case, we observed severe INH-induced immune thrombocytopenia that necessitated discontinuation of INH during the treatment of tuber-

**Table 1. Laboratory Findings of the Patient on Admission to Our Hospital.**

WBC (/μL)	4,900 (4,300-8,000)	TP (g/dL)	6 (6.6-8.1)
Neutrophils (%)	70.7 (49.5-71.0)	T-Bil (mg/dL)	1.4 (0.2-1.4)
Eosinophils (%)	8 (0.2-6.8)	AST (U/L)	39 (13-30)
Basophils (%)	0 (0.0-1.8)	ALT (U/L)	58 (8-42)
Lymphocytes (%)	15 (26.6-46.6)	LDH (U/L)	290 (124-222)
Monocytes (%)	8(2.3-7.7)	γ-GTP (U/L)	107 (13-64)
RBC (×10 <sup>4</sup> /μL)	459(450-510)	BUN (mg/dL)	22 (8-20)
Hemoglobin (g/dL)	6.4(12.4-17.2)	Cre (mg/dL)	1.3 (0.50-1.10)
Hematocrit (%)	18.4 (38.0-54.0)	Na (mEq/L)	130 (138-145)
Plt (×10 <sup>4</sup> /μL)*	1.5 (18.0-34.0)	K (mEq/L)	3.7 (3.6-4.8)
IPF (%)	24.7 (2.0-10.0)	Cl (mEq/L)	103 (101-108)
PT-INR	1.24	CRP (mg/dL)	2.05 (0-0.40)
APTT (sec)	55.7 (25.0-40.0)	HbA1c (%)	5.3 (4.6-6.2)
Fib (mg/mL)	76 (200-400)	PA-IgG (ng/10 <sup>7</sup> cells)	1,040
FDP (μg/mL)	7.8 (0-10.0)	HP-antibody	negative
D-dimer (μg/mL)	4 (0-1.0)	DLST	
Fe (μg/dL)	60 (40-188)	RFP	negative
Ferritin (ng/mL)	814.8 (39.9-465.0)	INH	positive
TIBC (μg/dL)	62 (250-410)		

WBC: white blood cells, RBC: red blood cells, Plt: platelets, IPF: immature platelet fraction, TP: total protein, T-Bil: total bilirubin, AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, γ-GTP: γ-glutamyl transpeptidase, BUN: blood urine nitrogen, Cre: creatinine, CRP: C-reactive protein, HbA1c: hemoglobin A1c, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, Fib: fibrinogen, FDP: fibrin/fibrinogen degradation products, Fe: ferrum, TIBC: total iron binding capacity, PA-IgG: platelet-associated immunoglobulin G, HP-antibody: *Helicobacter pylori* antibody, DLST: drug-induced lymphocyte stimulation test

\*Presence of aggregated platelets was not confirmed.

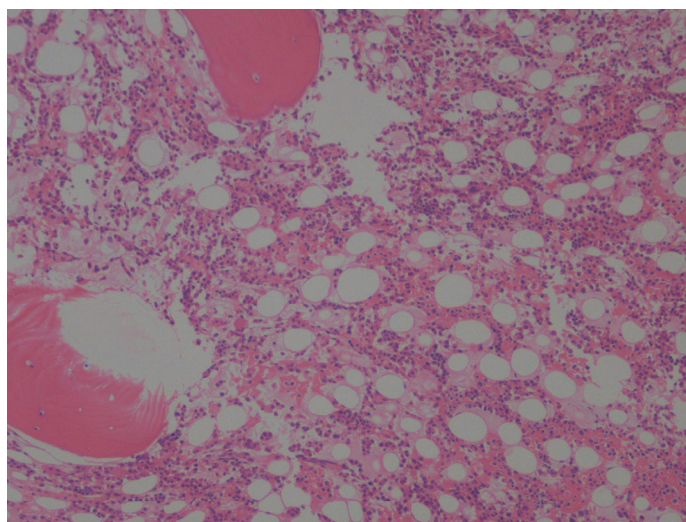


**Figure 2. Clinical course showing the association between the administered drugs and platelet count (A) before and (B) after the transfer to our hospital. INH: isoniazid, RFP: rifampicin, EB: ethambutol, PZA: pyrazinamide, LVFX: levofloxacin, SM: streptomycin, RBT: rifabutin, Plt: platelet**

culosis.

Antiplatelet antibodies are reportedly produced in the presence of the causative drug and bind to the platelet glycoprotein Ib/IX in RFP-induced immune thrombocytopenia (11). Although the mechanism underlying INH-induced immune thrombocytopenia remains unclear, a similar mechanism has been suggested.

Typically, symptoms occur when the platelet count drops below 20,000/mm<sup>3</sup>. Thrombocytopenia-related findings include ecchymoses, purpura, mucosal bleeding, and more serious hemorrhaging. In a review of 247 cases of drug-induced thrombocytopenia, 23 patients experienced major bleeding, including 2 who died of bleeding, while 60 patients were asymptomatic (12). A report showed that drug-



**Figure 3.** A histopathological examination of bone marrow showed the partial collection of hematopoietic cells and hypocellularity. No malignant or granulomatous findings were confirmed (Hematoxylin and Eosin staining,  $\times 100$ ).

**Table 2.** Criteria to Evaluate the Association between the Drugs and Thrombocytopenia (12).

Criterion	
1	1) Therapy with the candidate drug preceded thrombocytopenia and 2) recovery from thrombocytopenia was complete and sustained after therapy with the drug was discontinued.
2	1) The candidate drug was the only drug used before the onset or 2) other drugs were continued or reintroduced after discontinuation of therapy with the candidate drug with a sustained normal platelet count.
3	Other causes for thrombocytopenia were excluded.
4	Re-exposure to the candidate drug resulted in recurrent thrombocytopenia.
Level of evidence	
Definite	Criteria 1, 2, 3, and 4 met
Probable	Criteria 1, 2, and 3 met
Possible	Criterion 1 met
Unlikely	Criterion 1 not met

induced thrombocytopenia can occur more rapidly in patients with a history of causative drug administration than in those without such a history (13). This is presumably because patients sensitized by prior medication produce antibodies rapidly. For instance, severe RFP-induced thrombocytopenia occurs more quickly in patients with RFP re-administration or intermittent administration than in patients without RFP re-administration or intermittent administration (14, 15). In all cases of INH-induced thrombocytopenia, re-administration of INH was initiated after the discontinuation of anti-tuberculosis drugs (5-9), and the platelet count in 2 cases dropped below  $1 \times 10^4/\mu\text{L}$  (6, 7). Furthermore, in 1 of these 2 cases, re-administration commenced after an interval of 2 weeks, and the platelet count decreased to  $0.4 \times 10^4/\mu\text{L}$  within 2 days (7).

In patients administered multiple drugs, such as anti-tuberculosis, the identification of the causative drug is difficult. Furthermore, the exclusion of other etiologies is necessary for the diagnosis. George et al. suggested the criteria

for evaluating the association of drugs with thrombocytopenia (Table 2) (12). INH in the present case met criteria 1, 3, and 4, as pyrazinamide was discontinued before the discontinuation of INH. Therefore, the level of evidence set at “possible.”

A DLST can detect the proliferation of sensitized T-cells and is generally used for cases of type IV allergy, which results from T-cell-mediated immune responses. Antibody production in immune thrombocytopenia (previously known as idiopathic thrombocytopenia) is accelerated by CD4-positive helper T-cells (16). Therefore, a positive result on the DLST suggests that the mechanism of thrombocytopenia involves T-cell-mediated immune reaction. PA-IgG is a nonspecific antibody, and its titer does not correlate with thrombocytopenia severity (17). However, because its production is driven by helper T-cells, as mentioned above, it may have significance in cases with a positive result for the DLST. In two previous case reports of RFP- or INH-induced immune thrombocytopenia in which DLST and PA-IgG were tested,

PA-IgG was positive in both cases (6, 18), while the DLST was positive in one case (6). Although no studies have reported the significance of the DLST and PA-IgG in the diagnosis of drug-induced thrombocytopenia, these cases suggest the usefulness of DLST and PA-IgG.

The mainstay of treatment is the discontinuation of the suspected drug. For patients with severe thrombocytopenia or bleeding symptoms, platelet transfusions should be undertaken without delay. In such cases, it is critical to observe the effects of platelet transfusion, as the effect of transfusion is transient owing to the persistent destruction of donor platelets (19). Drug-induced thrombocytopenia is reversible. In most cases, the platelet count normalizes within approximately one week (16, 17, 20), while in this case it took over a week to improve because, as noted above, re-administration of the causative drug can cause severe thrombocytopenia. Furthermore, a case of long-term thrombocytopenia caused by re-administration of INH has been reported (6). Although corticosteroids are recommended for treating immune thrombocytopenia (21), their effects on drug-induced thrombocytopenia are controversial (20). However, corticosteroid use is permitted in drug-induced thrombocytopenia, as initially it is difficult to distinguish it from immune thrombocytopenia. Intravenous immunoglobulin infusion may be considered as an alternative therapy, although there are only a few such case reports (7, 22).

In conclusion, we experienced a case of INH-induced immune thrombocytopenia improved by the discontinuation of the drug. INH is an uncommon cause of thrombocytopenia; however, physicians should be aware that thrombocytopenia can be caused by INH.

**The authors state that they have no Conflict of Interest (COI).**

## References

- Hadfield JW. Rifampicin-induced thrombocytopenia. *Postgrad Med J* **56**: 59-60, 1980.
- Mehta YS, Jijin EE, Badakere SS, Pathare AV, Mohanty D. Rifampicin-induced immune thrombocytopenia. *Tuber Lung Dis* **77**: 558-562, 1996.
- Verma AK, Singh A, Chandra A, Kumar S, Gupta RK. Rifampicin-induced thrombocytopenia. *Indian J Pharmacol* **42**: 240-242, 2010.
- Dixit R, George J, Sharma AK. Thrombocytopenia due to rifampicin. *Lung India* **29**: 90-92, 2012.
- George JN. Platelets on the Web [Internet]. [cited 2020 Sep 20]. Available from: <https://www.ouhsc.edu/platelets/>
- Hansen JE. Hypersensitivity to isoniazid with neutropenia and thrombocytopenia. *Am Rev Respir Dis* **83**: 744-747, 1961.
- Hashiguchi N, Furuyama K, Kim M, Hirose N. A case of pulmonary tuberculosis complicated with severe thrombocytopenia during treatment. *Kekkaku* **87**: 345-349, 2012 (in Japanese, Abstract in English).
- Lee EJ, Lee SH, Kim YE, et al. A case of isoniazid-induced thrombocytopenia: recovery with immunoglobulin therapy. *Intern Med* **51**: 745-748, 2012.
- Yakar F, Yildiz N, Yakar A, Kılıçaslan Z. Isoniazid- and rifampicin-induced thrombocytopenia. *Multidiscip Respir Med* **8**: 13, 2013.
- Gupta P, Kumar H, Singh A, Srivastava UK, Verma AK, Chaudhary R. Isoniazid-induced thrombocytopenia in a patient with ocular tuberculosis. *Indian J Respir Care* **8**: 121-123, 2019.
- Pereira J, Hidalgo P, Ocqueteau M, et al. Glycoprotein Ib/IX complex is the target in rifampicin-induced immune thrombocytopenia. *Br J Haematol* **110**: 907-910, 2000.
- George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, Osborne S. Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med* **129**: 886-890, 1998.
- Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. *N Engl J Med* **357**: 580-587, 2007.
- Lee CH, Lee CJ. Thrombocytopenia - a rare but potentially serious side effect of initial daily and interrupted use of rifampicin. *Chest* **96**: 202-203, 1989.
- Mori M, Izawa K, Fujikawa T, et al. A case of acute and severe thrombocytopenia due to readministration of rifampicin. *J Infect Chemother* **17**: 288-290, 2011.
- Chong BH. Primary immune thrombocytopenia: understanding pathogenesis is the key to better treatments. *J Thromb Haemost* **7**: 319-321, 2009.
- Rousan TA, Aldoss IT, Cowley BD Jr, et al. Recurrent acute thrombocytopenia in the hospitalized patient: sepsis, DIC, HIT, or antibiotic-induced thrombocytopenia. *Am J Hematol* **85**: 71-74, 2010.
- Onoda T, Murakami K, Eda R, et al. Rifampicin-induced thrombocytopenia in a patient with miliary tuberculosis. *Kekkaku* **78**: 491-496, 2003.
- George JN, el-Harake MA, Raskob GE. Chronic idiopathic thrombocytopenic purpura. *N Engl J Med* **331**: 1207-1211, 1994.
- Pederson-Bjergaard U, Andersen M, Hansen PB. Drug-induced thrombocytopenia: clinical data on 309 cases and the effect of corticosteroid therapy. *Eur J Clin Pharmacol* **52**: 183-189, 1997.
- Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv* **3**: 3829-3866, 2019.
- Redall MA, Moore BR, Fass L. Use of i.v. immune globulin for presumed quinidine-induced thrombocytopenia. *Clin Pharm* **8**: 89, 1989.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).