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Case report

A case of immune thrombocytopenia due to miliary tuberculosis effectively treated with eltrombopag

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ABSTRACT

An 80-year-old woman was diagnosed with miliary tuberculosis. Laboratory findings showed marked thrombocytopenia (3000/μl). Immune thrombocytopenia (ITP) was diagnosed because platelet transfusion was ineffective, and bone marrow puncture demonstrated a normal number of megakaryocytes. Anti-tuberculosis treatment was started promptly, followed by prednisolone 20 mg. However, the platelet count did not increase. The effect of high-dose intravenous immunoglobulin was temporary. She was not responded to prednisolone, and eltrombopag 12.5 mg was added. The eltrombopag dose was increased by 12.5 mg every two weeks. When the eltrombopag dose reached 50 mg, the thrombocytopenia improved sufficiently (44,000/μl). She didn't have any severe bleeding and thrombotic complications. The treatment of tuberculosis went well and there was no side effect of anti-tuberculosis treatment. Eltrombopag can be a useful treatment for ITP due to tuberculosis.

1. Introduction

Immune thrombocytopenia (ITP) is characterized by thrombocytopenia due to an autoimmune mechanism. Various infectious and non-infectious conditions can be considered as factors causing ITP.

It is considered very rare that tuberculosis is associated with secondary ITP, though no prospective study investigating the prevalence of secondary ITP due to tuberculosis has been reported [1]. Many secondary ITP cases due to tuberculosis are usually treated with anti-tuberculosis treatment and corticosteroids, resulting in an increase of platelets from some days to 3 months [1]. Some cases of refractory ITP that required high-dose intravenous immunoglobulin (IVIG) have been reported [2]. However, there have been only one report of ITP due to tuberculosis that eltrombopag, thrombopoietin receptor agonist (TPO-RA), was administered [3].

We report a case of secondary ITP due to miliary tuberculosis in which anti-tuberculosis treatment and prednisolone had no effect, IVIG had only temporary and limited effects, and a gradual additional increase of eltrombopag seemed to be effective and safe.

2. Case report

An 80-year-old woman presented with a 1-month history of fever and appetite loss. Her chest computed tomography (CT) showed multiple miliary nodular shadows and some small cavitary lesions in all lung fields bilaterally (Fig. 1). Acid-fast bacteria staining of sputum was smear-positive, and tuberculosis was demonstrated in polymerase chain reaction (PCR) testing. The patient was diagnosed as having miliary tuberculosis and pulmonary tuberculosis. She was referred to our hospital and admitted to the isolation ward. She had mild mental retardation and a past history of an ovarian cyst.

On examination, her height was 152.1 cm, her weight was 42.0 kg, her temperature was 36.5 °C, her blood pressure was 115/74 mmHg, her pulse rate was 91 beats/min, and her oxygen saturation was 93%. She had anemic conjunctivae and purpura of the right inguinal region and left elbow joint, but no enlarged lymph nodes.

Chest and abdominal examinations showed no specific findings. Laboratory findings showed a normal white blood cell count, anemia (Hb 7.1 g/dl), marked thrombocytopenia (Plt 3000/μL), and elevated CRP (Table 1). Coagulation, liver function, and renal function tests were normal. There was no elevation of bilirubin, urinary urobilinogen. The urine and blood cultures for acid-fast bacteria were negative. Standard anti-tuberculosis treatment (isoniazid 300 mg, rifampicin 450 mg, ethambutol 500 mg, pyrazinamide 1200 mg) was started, along with platelet transfusion after bone marrow puncture at the time of admission. There was no increase of platelets (9000/μL) despite transfusion of 10 units of platelets for two days. In her myelogram, total nucleated cell counts were normal (184,750/μL), differential counts of granulocyte

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and erythroblast were normal, the megakaryocyte counts were almost normal (111/μL) and no blastoid cells were found. Bone marrow findings showed normal hematopoietic capacity and some epithelioid granulomas with caseating necrosis (Fig. 2). Acid-fast bacteria staining and culture of bone marrow were both negative. Immune thrombocytopenia (ITP) was diagnosed on the basis of the lack of efficacy of platelet transfusion and normal hematopoietic capacity. Anemia improved after transfusion 2 units of RCC. Anti-*Helicobacter pylori* (HP) antibody, anti-nuclear antibody, and hepatitis C antibody were all negative. Platelet-associated IgG was positive (53.9 ng/10^7 cells). Therefore, it was considered that the thrombocytopenia was secondary ITP due to miliary tuberculosis.

There was no increase of platelets despite initiation of prednisolone 20 mg on the third day. High-dose IVIG (20,000 mg/day, 476 mg/kg) was given for 5 days because anti-tuberculosis drugs and prednisolone 20 mg were ineffective. Laboratory findings showed temporary improvement of the platelet counts (56,000/μL) on the day 11, but the platelet counts dropped to less than 10,000/μL again in several days. Eltrombopag 12.5 mg, recommended initial dose in Japan, was then added on day 17. However, no platelet increase was achieved, and the eltrombopag dose was then increased by 12.5 mg every two weeks. After prednisolone 20 mg was given for 4 weeks, the dose of prednisolone was decreased to 10 mg for three weeks. Sufficient elevation of the platelets (44,000/μL) was seen when the dose of eltrombopag reached 50 mg on day 65 (Fig. 3). The patient had no bleeding complications and no thrombotic diseases during hospitalization. During the treatment of tuberculosis, the major side effects, including liver dysfunction and rash, were not observed. The respiratory condition gradually improved in the initial two weeks. The drug sensitivity test for *Mycobacterium tuberculosis* showed that it was sensitive to all anti-tuberculosis drugs. The anti-tuberculosis drugs were decreased to the two drugs isoniazid and rifampicin on day 68. The sputum smear staining showed negative conversion at 5 weeks. A chest X-ray showed improvement of the miliary nodular shadows. She was discharged to her house on day 71. It was

Table 1
Laboratory findings on admission.

Hematology			Biochemistry		
WBC	6530	/μL	TP	7.3	g/dL
Neutrophils	68.9	%	Albumin	2.3	g/dL
Lymphocytes	24.8	%	total birilubin	0.8	mg/dL
Monocytes	5.5	%	AST	31	IU/L
Eosinophils	0.6	%	ALT	15	IU/L
Basophils	0.2	%	LDH	294	IU/L
Hematocrit	23.8	%	ALP	276	IU/L
Hemoglobin	7.1	g/dL	CK	20	U/L
RBC	25,10,000	/μL	AMY	49	U/L
Platelets	4000	/μL	BUN	16	mg/dL
			CRE	0.93	mg/dL
Coagulation			UA	5.4	mg/dL
Prothrombin time	11.6	sec	Ca	8.2	mg/dL
APTT	40	sec	Na	137	mEq/dL
Fibrinogen	161	mg/dl	K	3.4	mEq/dL
D-dimer	11.4	μg/mL	Cl	102	mEq/dL
Serology			CRP	2.67	mg/dL
antinuclear antibody	< 40	liter	HbA1c	4.9	%
Hepatitis C antibody	negative				
anti H.pyroli antibody	5.4	IU/mL	PT-IgG	53.9	ng/107 cells

RBC: red blood cell, ESR: erythrocyte sedimentation rate, TP: total protein.
AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, CK: creatine phosphokinase.
AMY: amylase, BUN: blood urea nitrogen, CRE: creatinine, CRP: C reactive protein.
APTT: Activated partial thromboplastin time, PT-IgG: platelet associated immunoglobulin G.

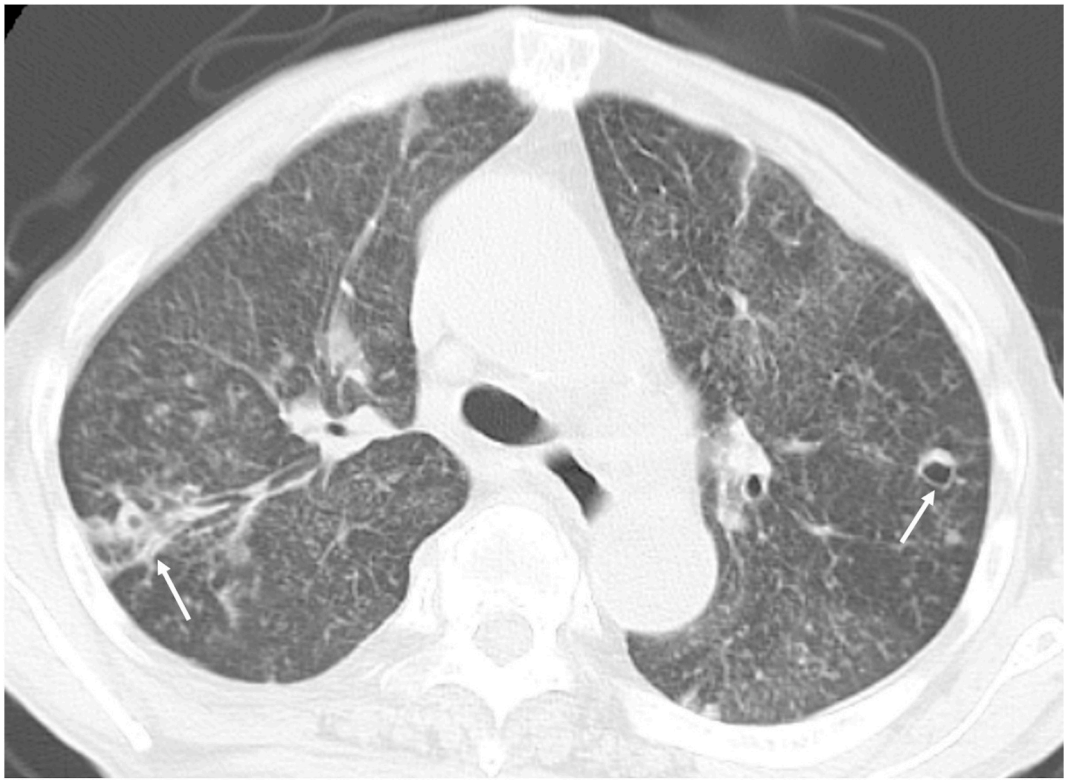

Fig. 1. Chest CT on admission.
Chest CT shows multiple miliary nodular shadows and some small cavitary legions in all lung fields bilaterally. The arrows indicate some small cavitary lesions.

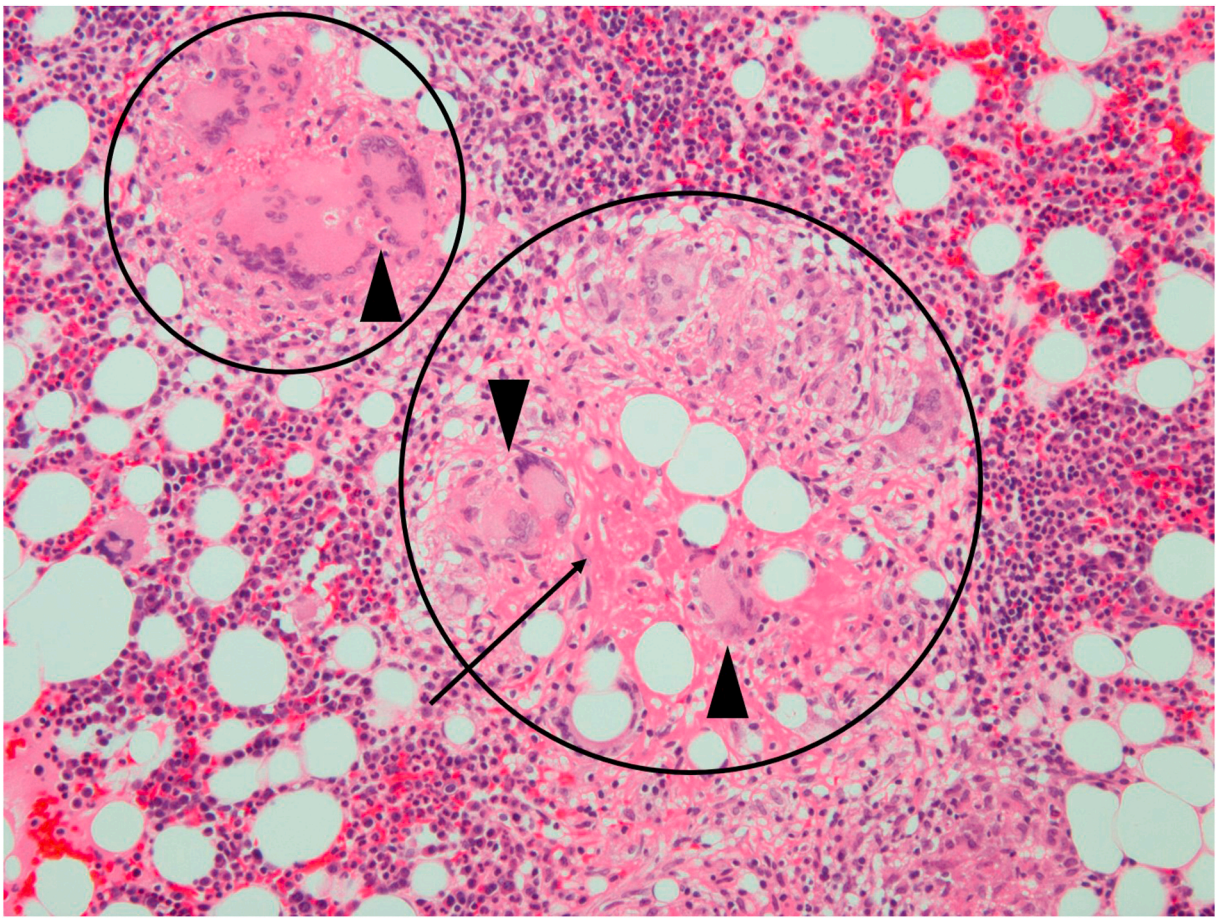

Fig. 2. Histopathological findings of bone marrow (hematoxylin-eosin stain × 100).
Histopathological findings of bone marrow from the right iliac crest show normal bone marrow and some epithelioid granuloma with caseating necrosis. The arrow indicates the caseating necrosis. The arrowheads indicate epithelioid cells. The circles indicate some epithelioid granuloma.
Acid-fast bacteria staining and culture of bone marrow were both negative.

planned to give the patient standard anti-tuberculosis treatment for an extra 3 months (total 9 months) because of steroid use and the presence of miliary tuberculosis.

3. Discussion

This present case demonstrates that additional eltrombopag can be an effective and practical treatment in secondary ITP due to tuberculosis not responded to prednisolone and anti-tuberculosis treatment. This is important information for physicians because secondary ITP due to tuberculosis is considered a treatable disorder that responds to corticosteroids, and anti-tuberculosis treatment.

Her thrombocytopenia is existing in the diagnosis of tuberculosis and she didn't have concurrent medication. Bone marrow involvement with tuberculosis is conceivable as a reason for thrombocytopenia, because she had caseating granuloma in her bone marrow. However, the diagnosis in the present case was ITP, considering that platelet transfusion was not effective, and there was no decrease of megakaryocytes, normal hematopoietic capacity in her bone marrow. In our view, bone marrow involvement of tuberculosis didn't contribute much to thrombocytopenia clinically. We think she didn't suffer from Evan's syndrome in the absence of hemolysis and improvement of anemia by transfusion. We ruled out hemophagocytic lymphohistiocytosis (HLH) because of no splenomegaly, fibrinogen 161 mg/dl (more than 150 mg/dl), and no HLH in the bone marrow findings. Moreover, we ruled out Disseminated intravascular coagulation because of normal prothrombin time (11.6 sec), activated partial thromboplastin time (40 sec), fibrinogen, that is no hypercoagulable condition.

We ultimately diagnosed her as ITP due to tuberculosis because she didn't have connective tissue disease and other infectious diseases due to ITP. The platelet counts were marked low value, and the patient presented with severe anemia. She had subcutaneous bleeding without apparent wet purpura. But we couldn't completely rule out wet purpura including gastrointestinal bleeding at the admission because we didn't know the progression of anemia. Therefore, we considered the necessity of treating ITP.

No established standard therapy for ITP due to tuberculosis has been recognized. Weber et al. reported a case and a review of secondary ITP due to tuberculosis. Anti-tuberculosis treatment and corticosteroids are effective in many cases. High-dose IVIG is sometimes used with corticosteroids. The prognosis of ITP due to tuberculosis is generally good. Weber et al. concluded that early diagnosis and initiation of treatment for tuberculosis should be given the highest priority to reduce the use of immunosuppressants, transfusion, and the risk of hemorrhage [1]. There are 4 new case reports of ITP due to tuberculosis after Weber's report [4–7]. Considering 50 cases and 4 cases, most cases obtain platelets response using anti-tuberculosis treatment, corticosteroid and IVIG. Time from treatment initiation until platelets recovery varies from some days to a few months. No severe fetal bleeding occurred in the clinical course [1,4–7].

Anti-tuberculosis treatment combined with high-dose IVIG were reported to be safe and effective for ITP due to tuberculosis. The effect of high-dose IVIG was obtained in a few days [8,9]. In the present case, an early increase of platelets was seen with high-dose IVIG, but it was not

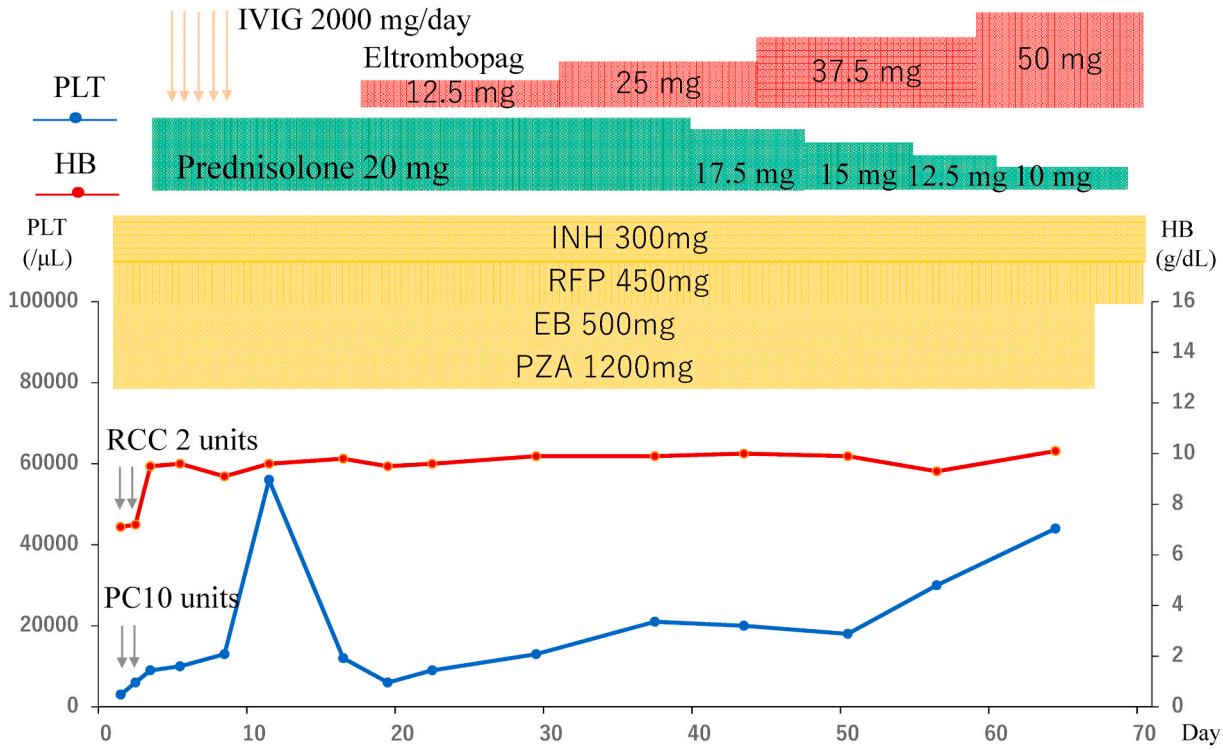

Fig. 3. Clinical course.
This figure shows the clinical course and changes in hemoglobin and platelet counts.
The red line shows hemoglobin (Hb). The blue line shows the platelets (PLT). IVIG: intravenous immunoglobulin therapy. INH: isoniazid. RFP: Rifampicin. EB: ethambutol. PZA: pyrazinamide.

sustained.

The standard first-line treatment for primary ITP is mainly corticosteroids. At least 80% of patients with ITP showed an initial response to corticosteroids. Intravenous immunoglobulin is often used when a rapid rise in the platelet count is desired [10]. There are several second-line treatments for corticosteroid-resistant ITP. TPO-RA, splenectomy, and rituximab are recommended, and the choice of these second line treatments should be based on the individual situation [11].

In adults, the treatments of secondary ITP differ depending on the underlying disease. Corticosteroids and splenectomy are less effective in secondary than in primary ITP [12]. Secondary ITP with infectious diseases has no tendency to remit spontaneously, although the severity of the thrombocytopenia may parallel the stage of the infectious disease [13]. Patients with HCV infection and immune thrombocytopenia have been reported to have a greater than 50% platelet response to corticosteroids [13,14]. In Rajan's report, of the seven patients treated with prednisone, four (55.7%) responded, and six developed elevations of hepatic transaminases of two times greater than pretreatment levels while receiving prednisone [15]. In patients with HIV infection, antiretroviral therapy is the first-line and most effective treatment [13,14]. In addition, HIV-associated thrombocytopenia is generally responsive to the therapies used in classical ITP [13]. In *H pylori*-infected ITP patients, eradication therapy obtains an overall response in 52.7% of patients [13]. However, prolonged corticosteroid usage has a potential adverse effect on the underlying infection [14].

Eltrombopag is an oral TPO-RA and works on the stem cells and megakaryocytes and increases platelet counts. Eltrombopag is positioned as the second-line therapy for adult primary ITP [14]. The RAISE study demonstrated that eltrombopag had more efficacy in previously treated ITP than placebo over a 6-month period [16]. The EXTEND study demonstrated that eltrombopag had infrequent important adverse events [17]. The role of eltrombopag in secondary ITP is not established. Gonzalez-Lopez et al. reported the use of eltrombopag for secondary ITP in clinical practice. In their report, of 87 secondary ITP patients who had been treated with eltrombopag, 44 (51%) had a platelet response, including 40 (46%) with complete response. The median time to platelet response was 15 days (95% confidence interval, 7–28 days), and the platelet response rate was significantly lower in lymphoproliferative disorders than in autoimmune diseases and infectious diseases. Forty-three patients (49.4%) experienced adverse events (mainly grade 1–2), the most common being hepatobiliary laboratory abnormalities. Eltrombopag is effective and well-tolerated in unselected patients with ITP secondary to both immune and infectious disorders [12]. But there has been only one report in which eltrombopag was administered for ITP due to tuberculosis. In Surana's case, high dose dexamethasone and anti-rh0 immunoglobulin were minimal transit response, and the administration of eltrombopag 50 mg led to the rapid response of platelets [3].

In the present case, prednisolone 20mg is too low because prednisolone 0.5mg/kg is a small dose as the treatment of ITP and the effect of prednisolone decreases under combination with rifampicin inducing cytochrome p450 3A4 (CYP3A4). We placed maximum priority on tuberculosis treatment. We had to start prednisolone early because we evaluate the patient had bleeding tendency. But we worried the deterioration of tuberculosis and considered she might resolve with tuberculosis treatment alone. Therefore, we decided to use low dose prednisolone.

A low dose of prednisolone may be one of the reasons that antituberculosis treatment and prednisolone were not effective for ITP due to tuberculosis. In adults with newly diagnosed ITP, the ASH guideline panel suggests either prednisone (0.5–2.0 mg/kg per day) or dexamethasone (40 mg per day for 4 days) as the corticosteroid for initial therapy [6]. In the treatment of secondary ITP due to tuberculosis, the most important aim is curing tuberculosis. We didn't use high-dose and long-term corticosteroids and administered eltrombopag early to avoid that tuberculosis got worse. We initiated 12.5 mg of eltrombopag and

increased the dose every two weeks according to package insert in Japan.

Dhibar DP et al. claimed IV pulse of methylprednisolone along with anti-tuberculosis treatment might be given after judging the risk and benefit in resource constraint settings [18]. We think eltrombopag should be used in only patients with strong bleeding tendency and resistant to anti-tuberculosis treatments and corticosteroids. Anti-tuberculosis treatment and prednisolone could be useful in many cases. We should wait with using only anti-tuberculosis treatment and prednisolone until recovery of platelets in resource constraint settings.

There are some possibilities that may explain why it took a long time to increase platelet counts in the present case. First, the dose of prednisolone may have been too low. Second, the initial dose of eltrombopag may have been too low. Third, the anti-tuberculosis treatment takes time to have an effect on ITP independently from eltrombopag. We don't know eltrombopag was effective for ITP due to tuberculosis alone, but low dose prednisolone, anti-tuberculosis treatment and early administered eltrombopag resulted in the increase of platelets and no influence for tuberculosis treatment. Although the recommended initial dose of eltrombopag is 12.5 mg in Japan, the higher initial dose may be better.

Eltrombopag was effective for ITP due to tuberculosis in which anti-tuberculosis treatment, corticosteroids, and high-dose IVIG were ineffective. There were no major or minor side effects. We prefer to avoid immunosuppressants for anti-tuberculosis treatment and corticosteroids-resistant ITP due to tuberculosis. In such cases, additional eltrombopag can be a useful and safe option.

In our view, corticosteroids and anti-tuberculosis treatment should be used in combination, in the treatment of ITP due to tuberculosis. If this is not effective, eltrombopag should be administered early in the treatment of ITP due to tuberculosis. These treatments can be an effective and safe treatment without negative impact on tuberculosis treatment. It is strongly expected that additional cases using eltrombopag in secondary ITP cases due to tuberculosis are reported. In conclusion, the second case in which additional eltrombopag was effective for an elderly woman with ITP due to miliary tuberculosis not responded to prednisolone and anti-tuberculosis treatment was described. Eltrombopag may have an advantage in ITP secondary to tuberculosis in which anti-tuberculosis treatment, corticosteroids and high-dose IVIG are ineffective.

Declaration of competing interest

The authors state that they have no conflict of interest to declare.

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