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Case Report and Review of the Literature

The Development of Acquired Amegakaryocytic Thrombocytopenia in a Patient with Idiopathic Thrombocytopenic Purpura

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ABSTRACT

A 67-year-old Japanese male patient with *Helicobacter pylori* infection developed severe thrombocytopenia and was diagnosed with primary immune thrombocytopenia (ITP) on December 22, 2021. He was treated with *Helicobacter pylori* eradication therapy, corticosteroids, and eltrombopag (ELT). The platelet count (PLT) improved rapidly; however, after ELT cancellation and corticosteroid reduction, the PLT swiftly decreased. When the corticosteroid dose was increased, the PLT rapidly increased. The corticosteroid dose was reduced immediately; however, the patient presented with subacute arterial obstruction in the right leg and ultimately underwent surgical thrombectomy and transmetatarsal amputation. After corticosteroid cancellation, the PLT again decreased swiftly. Corticosteroids and ELT were thus re-administered. The PLT showed a tendency to recover temporarily, although the drug reaction was not gradual and showed a tendency to decrease. After a repeated BM aspiration, only megakaryocytes were not detected. We determined that the pathogenesis of the severe thrombocytopenia converted from ITP to acquired amegakaryocytic thrombocytopenia (AAMT). Cases of a conversion from ITP to AAMT are extremely rare, and the mechanism underlying this conversion is not well understood. Herein, we report the first case, to the best of our knowledge, in which transmetatarsal amputation triggered the progression of ITP to AAMT.

Introduction

Acquired amegakaryocytic thrombocytopenia (AAMT) is a rare hematological disorder characterized by reduced or absent megakaryocytes (Mgks) in the bone marrow (BM). It is speculated that the incidence of AAMT is higher than the case numbers generally recognized because it is frequently misdiagnosed as immune thrombocytopenia (ITP) [1]. However, it is extremely rare that the pathogenesis of thrombocytopenia converts from ITP to AAMT; only three reports, to the best of our knowledge, have shown this [2-4].

In this case study, we present a fourth patient who converted from ITP to AAMT. The first patient in the literature was treated with a combination of plasmapheresis and vinblastine infusion. This combination therapy promptly resulted in a rise in the platelet count (PLT). However, the effective treatment period was relatively short. The second patient had ITP with hepatitis C. When this patient died of liver failure, autopsy showed that it was AAMT, not ITP [3]. The third patient was diagnosed with ITP. Splenectomy was performed because of prednisolone (PSL) resistance. The PLT rapidly increased but decreased again. The BM examination revealed a conversion to AAMT. The patient then periodically repeated AAMT [4]. In our patient, ITP became refractory after amputation of the right metatarsal, and then converted to AAMT. Three mechanisms have been suggested to explain the onset of AAMT: i) maturational restraint of Mgks by external factors, such as hepatitis C and cytomegalovirus infection; ii) maturational restraint of Mgks by endogenous stimulation or T cell-related autoimmunity; and iii) initial symptoms of stem cell abnormalities. No external factors or stem cell abnormalities were observed in this case.

The AAMT in our patient appeared to develop due to endogenous stimulation or T cell-related autoimmunity. The autoantibody against glycoprotein (GP)IIb/IIIa is the most influential factor in platelet

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destruction in ITP [5, 6]. In contrast, the ultrafine morphology of Mgks in patients with ITP demonstrates characteristics of apoptosis, such as mitochondrial swelling, autophagic vacuolization, and chromatin aggregation [7]. This suggests that ITP involves not only the peripheral destruction of platelets, but also a platelet-producing obstacle. Anti-thrombopoietin (TPO) receptor (c-MPL) antibodies inhibit the binding of the ligand to c-MPLs on stem cells and Mgks, resulting in the inhibition of the TPO signal. The anti-c-MPL antibody is thought to be a functional autoantibody that induces AAMT [8]. Thus, thrombocytopenia in ITP or systemic lupus erythematosus (SLE) is thought to be caused simultaneously by the destruction of platelets and restraint of Mgk maturation, which are individually mediated by two types of autoantibodies [9].

However, patients with ITP usually do not have sufficient anti-c-MPL antibody titers to induce AAMT [10]. Among the three case reports in which ITP converted to AAMT, one showed that hepatitis C might be the main factor in the conversion. However, the others did not have any meaningful factors. We encountered a rare case of transmetatarsal amputation for extensive toe necrosis that converted from ITP to AAMT. Here, we report this case along with a literature review.

Case Presentation

A 67-year-old male patient was hospitalized with severe thrombocytopenia (Table 1). He was diagnosed with *Helicobacter pylori*-associated ITP based on an increase in the number of Mgks in the BM (Figure 1A), high serum anti-*Helicobacter pylori* immunoglobulin (Ig) G antibody titers, and the presence of atrophic gastritis. The PLT rapidly recovered after treatment with *Helicobacter pylori* eradication therapy and PSL. The PLT then completely recovered, even after tapering the PSL dose using eltrombopag (ELT). After canceling the treatment with ELT owing to hepatic dysfunction, the PLT rapidly decreased. Reinfection with *Helicobacter pylori* was not detected; however, the BM image was compatible with ITP. After increasing the quantity of PSL and using ELT in combination, a rapid increase in the PLT was observed. The patient presented with right toe necrosis due to arterial thrombosis of the lower extremity and underwent amputation of the right metatarsal bone.

Table 1: Blood test. At onset of ITP (December 23, 2023).

Complete Blood Count		Biochemistry test		Serological test		Bone marrow	
WBC	3,100/μ*l*	TP	7.4 g/d*l*	ANA	<40	NCC	26.1×10^4/μ*l*
Segmented neutrophil	63.0%	Alb	4.4 g/d*l*	aCL-β2GP1	≦1.2	MgK	135/μ*l*
lymphocyte	26.0%	AST	52 U/*l*	aCL	≦8	Pro.E	0.2%
Monocyte	9.5%	ALT	60 U/*l*	LA dRVVT	≦1.2	Ba.E	4.2%
Basophilic	1.0%	ALP	358 IU/m*l*	anti HP IgG Ab	25 U/m*l*	Poly.E	22.0%
Atypical lymphocyte	0.5%	γ-GTP	113 IU/*l*	HCV Ab	(-)	Orth.E	0.8%
RBC	426×10^4/μl	LDH	250 U/*l*	HBs Ag	(-)	M.Bla	1.2%
Hb	13.6 g/dl	T-bil	1.4 mg/d*l*	IgG	857 mg/d*l*	Pro	3.2%
Ht	39.2%	D-bil	0.5 mg/dl	IgA	118 mg/d*l*	Myelo	13.2%
MCV	92.0 f*l*	BUN	4.7 mg/d*l*	IgM	780 mg/d*l*	Meta	5.2%
Plt	1.0×10^4/μ*l*	Cr	0.75 mg/d*l*	FLC κ/λ ratio	8.59	Stab	9.8%
		UA	3.6 mg/dl	PAIgG	2190 ng/10^7cells	Seg	23.4%
Urinalysis		T-CHO	192 mg/d*l*			Eo	2.8%
Color	yellow	TG	69 mg/d*l*	Coagulation		Ba	0.2%
Protein	(±)	glu	100 mg/d*l*	PT-INR	1.03	Ly	10.4%
Glucose	(-)	HbA1c	5.3%	APTT	29.5	Mo	2.4%
Occult blood	1(+)	Na	142 mEq/*l*	Fibrinogen	525.8	Plasma	0.8%
		K	3.5 mEq/*l*	FDP	≦2.5	MΦ	0.2%
		Cl	108 mEq/*l*	D-dimer	0.7 ng/m*l*	M/E	2.3%
		CRP	2.01 mg/d*l*			chromosome 46 X, Y	

Once treatment with PSL and ELT was discontinued, the PLT swiftly decreased again. After readministering PSL and ELT, a rise in the PLT was soon observed, although the PLT remained approximately 1.5×10^4/μL and gradually decreased. The patient became resistant to ELT and PSL and required frequent platelet transfusions. In addition, because of the progression of anemia due to the bleeding tendency, the patient occasionally required red blood cell transfusions. There is a report that tirabrutinib, a newly developed Bruton's tyrosine kinase inhibitor approved for waldenstrom macroglobulinemia (WM), lymphoplasmacytic lymphoma, and primary central nervous system lymphoma in Japan, is effective for refractory ITP with IgM-monoclonal gammopathy of undetermined significance (MGUS) [9]. However, recovery of the PLT with tirabrutinib treatment was not observed in our case (Figure 2A).

Reexamination of the BM barely detected Mgks (Figure 1B). Consequently, the patient was diagnosed with AAMT (Table 2). We initiated the patient on immunosuppressive therapy using human/rabbit anti-thymocyte immunoglobulin (ATG), cyclosporine, and methyl-PSL together with romiplostim. Because the counts of white blood cells and reticulocytes decreased rapidly after immunosuppressive therapy was initiated, the patient received lenograstim daily and frequent red blood cell transfusions. BM examination did not detect any Mgks (Figure 1C). We detected an improvement in pancytopenia two months after the initiation of immunosuppressive therapy (Figure 2B).

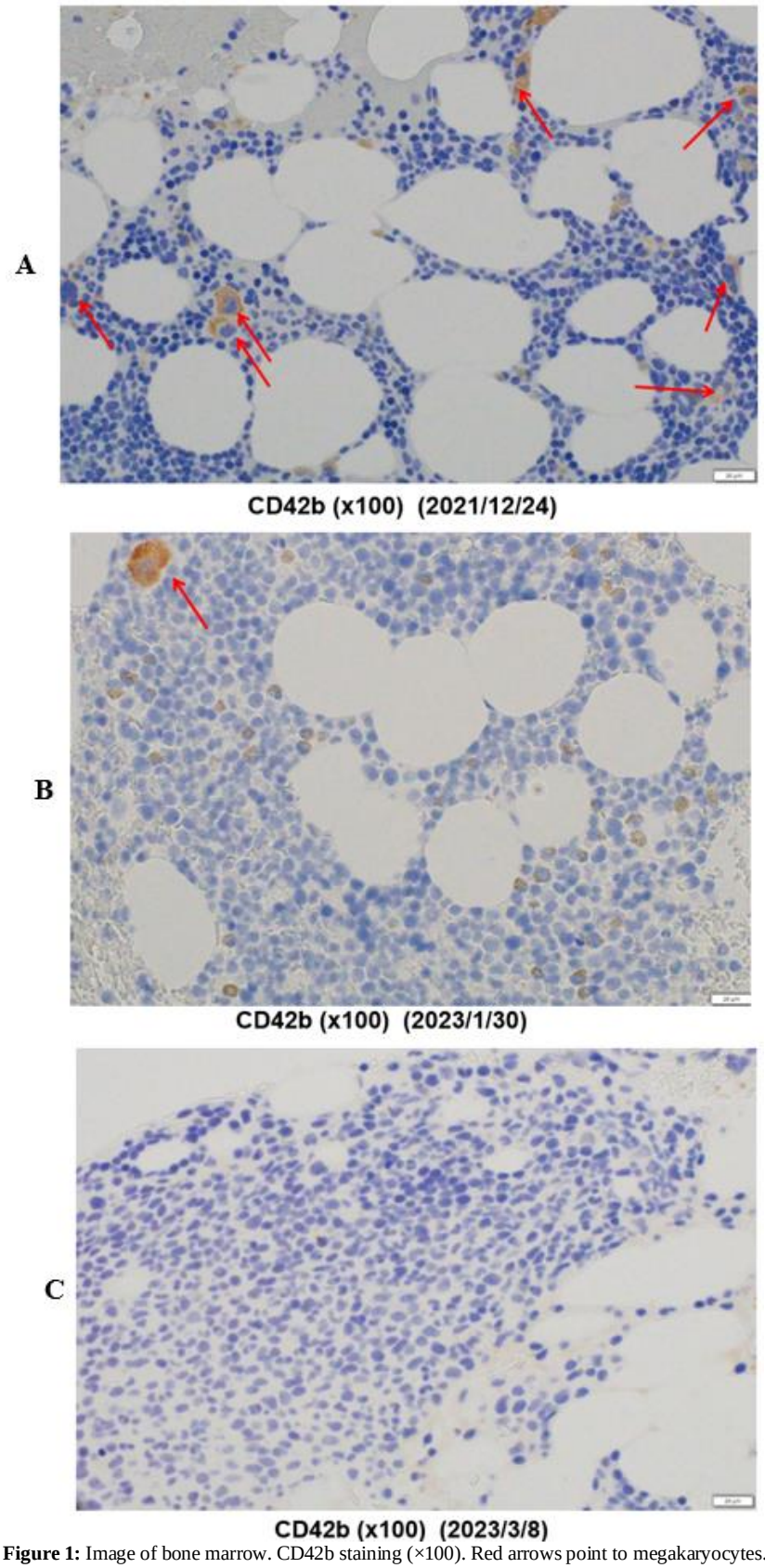

Figure 1: Image of bone marrow. CD42b staining (×100). Red arrows point to megakaryocytes.
A) At onset of ITP (December 24, 2023). **B)** When all treatments for ITP have failed (January 30, 2023). **C)** Five weeks after starting immunosuppressive therapy (March 8, 2023).

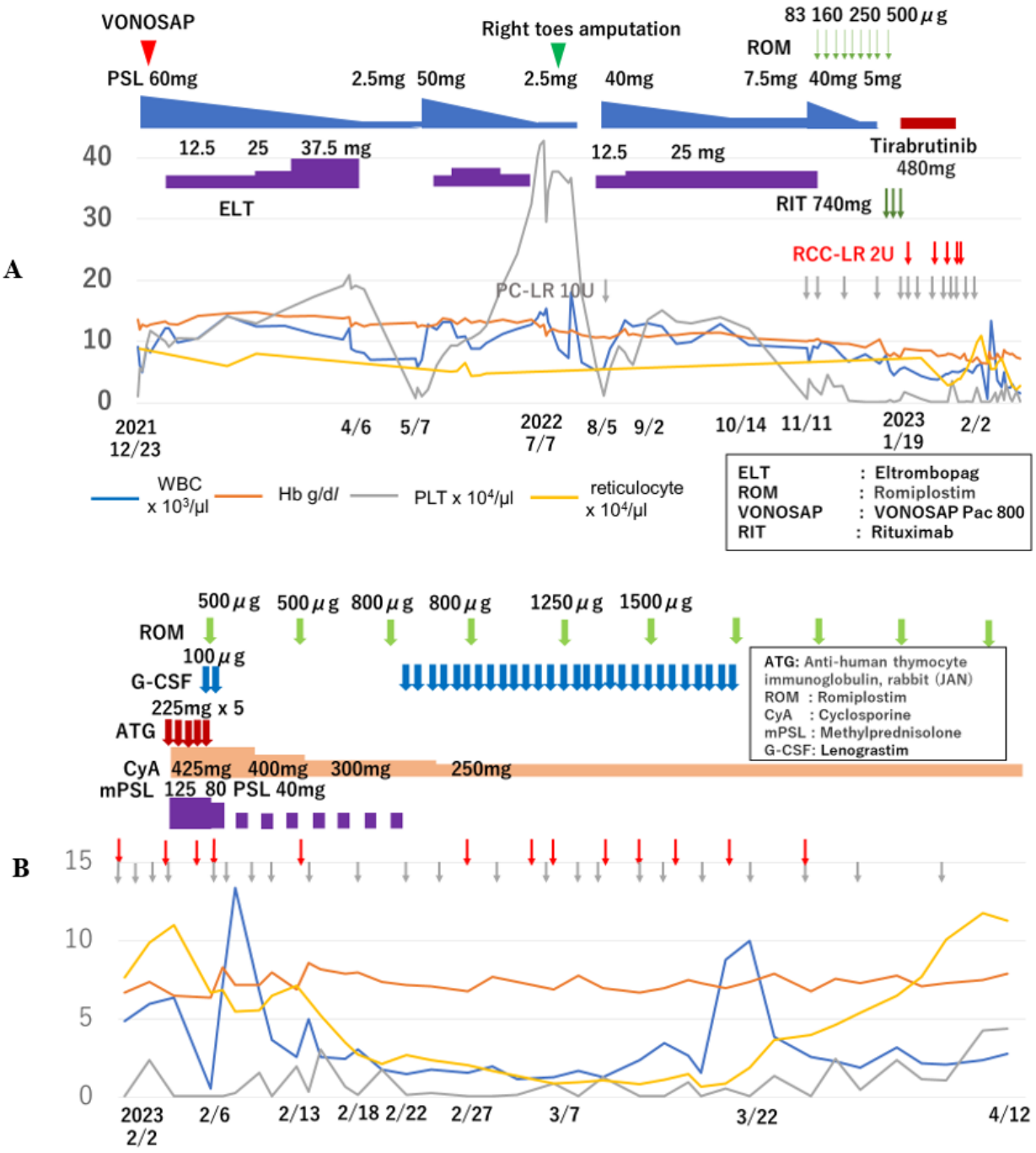

Figure 2: Clinical course. **A)** Clinical course until ITP becomes refractory. **B)** Clinical after immunosuppressive therapy.

Table 2: Blood test. When all treatments for ITP have failed (January 30, 2023).

Complete Blood Count			Biochemistry test			Bone marrow	
WBC	4,800/μl		Alb	3.8 g/dl		NCC	30.0 × 10^4 /μl
Segmented neutrophil	49.8%		AST	16 U/l		MgK	<15 /μl
lymphocyte	19.6%		ALT	9 U/l		Pro.E	0.2%
Monocyte	17.3%		ALP	72 IU/ml		Ba.E	3.0%
Basophilic	1.0%		γ-GTP	24 IU/l		Poly.E	14.8%
Atypical lymphocyte	0.5%		LDH	251 U/l		Orth.E	0.6%
RBC	226 x 10^4/μl		T-bil	2.1 mg/dl		M.Bla	2.2%

Hb	6.7 g/dl		BUN	9.4 mg/d*l*		Pro	3.0%
Ht	21.5%		Cr	0.87 mg/d*l*		Myelo	11.2%
MCV	95.1 f*l*		UA	3.3 mg/dl		Meta	11.8%
Plt	$<0.1 \times 10^4/\mu l$		glu	98 mg/d*l*		Stab	15.6%
reticulocyte	$7.684 \times 10^4/\mu l$		HbA1c	5.4%		Seg	18.6%
Urinalysis			Na	146 mEq/*l*		Eo	6.0%
Color	yellow		K	3.4 mEq/*l*		Ba	0.0%
Protein	(±)		Cl	114 mEq/*l*		Ly	7.2%
Glucose	(-)		CRP	0.37 mg/d*l*		Mo	4.8%
Occult blood	1(+)					Plasma	0.6%
			Serological test			MΦ	0.0%
			TPO	26.1		M/E	3.68
						chromosome 46 X, Y	

Discussion

Four mechanisms have been suggested for the onset of AAMT. The first is the maturational restraint of Mgks by external factors, such as viral infections, toxin exposure, nutritional deficiencies, drug ingestion, alcohol excess, and previous radiotherapy of the BM [11-14]. The second is suppression of Mgk maturation by endogenous stimuli due to antibody-mediated or T-cell autoimmunity, such as thymoma, with a more aggressive disease course; adult-onset still disease; eosinophilic fasciitis; SLE; systemic sclerosis; Graves' disease; and hyperestrogenic states [12, 15-17]. The third is an early manifestation of a stem cell abnormality, such as a precursor to acute myeloid leukemia, myelodysplastic syndrome, aplastic anemia, or non-Hodgkin's lymphoma [18, 19]. The fourth is the replacement of normal marrow constituents with infiltrative or malignant processes.

Because our patient had ITP as an underlying disease, antibody-mediated endogenous stimulation was considered the cause for the onset of AAMT. However, there are few reports of cases where a conversion to AAMT occurred through the progression of ITP. To the best of our knowledge, only three such studies have been published to date. The first patient converted to AAMT without a specific cause during an episode of ITP care [2]. The second patient was diagnosed with hepatitis C-mediated ITP [3]. When this patient died of liver failure, he was diagnosed with AAMT by autopsy. It was hypothesized that hepatitis C was the cause of AAMT onset. The third patient with ITP had a temporary recovery of PLT after splenectomy, but was then converted into AAMT and periodically repeated it.

Our patient with ITP underwent metatarsal bone amputation for toe necrosis caused by a lower-limb artery clot. Subsequently, he converted to AAMT. There have been no reports, to the best of our knowledge, that thrombosis, necrosis, and bone amputation were causes for AAMT onset, although we cannot exclude the possibility that these resulted in an external factor and endogenous stimulation leading to the onset of AAMT.

Two types of autoantibodies act on thrombocytopenia, based on autoimmune diseases such as ITP and SLE. If GPIIb/IIIa on the platelet surface become the target, the platelet destruction in the reticuloendothelial system predominates [5, 6]. If c-MPL on the surface of Mgks is targeted, platelet production failure predominates. c-MPL is present on the surfaces of Mgks and hematopoietic stem cells. Anti-c-MPL antibodies inhibit the maturation and production of Mgks [9]. In thrombocytopenia with autoimmune disease, platelet destruction, which targets GPIIb/IIIa, is the main constituent. It is speculated that the production of sthenia of the anti-c-MPL antibody following some kind of stimulation participates in a conversion to AAMT. Measurement of the anti-c-MPL antibody titer is useful for the differential diagnosis of AAMT and ITP. However, they cannot be regularly inspected. The blood TPO level markedly increases in patients with AAMT, as well as aplastic anemia. In contrast, the blood TPO level in patients with ITP is only slightly higher than that in healthy individuals, despite a significant decrease in the PLT [20]. Blood TPO levels are not high in ITP because abundant Mgks adsorb the majority of the TPO. This is consistent with the finding of a past report.

AAMT does not usually respond to standard therapies, such as corticosteroid use and intravenous Ig infusion. Our patient was resistant to the steroids, eltrombopag, romiplostim, and rituximab. Tirabrutinib is a molecular-targeted drug effective against WM. As our patient did not show BM infiltration of lymphoplasmacytes and did not have an *MYD88* genetic mutation, he was diagnosed with IgM MGUS. Patel *et al.* confirmed the presence of platelet-associated (PA) IgM in patients with WM [21]. The authors reported that IgM causes thrombocytopenia. IgM antibodies form immune complexes or attach to platelet-bound IgG in a manner analogous to that of rheumatoid factors. PA IgM has also been observed in some patients with ITP with or without coexisting PA IgG [22]. Tirabrutinib has been reported to be effective for refractory ITP with IgM-MGUS [10]. However, this treatment was ineffective in the present case. A BM smear showed that the cause of thrombocytopenia had converted from ITP at that time.

After diagnosis, AAMT develops into aplastic anemia within an average of one month to two years. Patients with aplastic anemia have a poor prognosis [23]. Therefore, once AAMT is diagnosed, treatment should be initiated immediately. Our patient showed a decreasing tendency in the counts of white blood cells and reticulocytes from an early stage of immunosuppressive therapy, suggesting progression to aplastic anemia. Hoffman recommended plasmapheresis and therapy using cyclophosphamide, cyclosporine, and PSL for antibody-mediated AAMT and treatment using cyclosporine, cytokines, and ATG for T-cell-mediated AAMT [11]. Although the participation of the anti-c-MPL antibody was suggested as a mechanism of the conversion from ITP to

AAMT, the administration of rituximab and PSL, which inhibit antibody production, was not effective in our patient. These findings suggest that the main pathological constituent of AAMT in our patient may have been T-cell-mediated autoimmunity. As expected, a tendency to recover from pancytopenia was observed approximately two months after the initiation of immunosuppressive therapy in our patient, including that using ATG, and the patient ultimately did not need blood transfusion.

To date, only three cases of AAMT in ITP have been reported to our knowledge. The participation of hepatitis C in the progression of AAMT was suggested in one patient. In contrast, direct induction was not observed in the other two patients. Our patient was the fourth patient and converted to AAMT after metatarsal bone amputation. Accumulation of such cases is needed in the future to clarify the cause and mechanism of the conversion from ITP to AAMT. In addition, when ITP becomes intractable during standard treatment, we should question a conversion to AAMT and BM reexamination should be conducted.

Data Availability

All data are available in the hospital's medical records.

Conflicts of Interest

Submitting authors are responsible for coauthors declaring their interests.

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