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Case Report

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Acquired Amegakaryocytic Thrombocytopenic Purpura that Presented as Cyclic Thrombocytopenia Associated with Anti-Phospholipid Antibody Syndrome

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Abstract

A 52-year-old female, who had been taking prednisolone (PSL) for anti-phospholipid antibody syndrome (APS), was admitted to our hospital because of repeated nasal bleeding, purpura and petechiae of the extremities, and a platelet count of 7,000/μL. The PSL dose was increased due to a tentative diagnosis of idiopathic thrombocytopenic purpura (ITP), but she presented with cyclic thrombocytopenia independent of the PSL dose and repeated nasal, oral, and gastrointestinal bleeding. Then, she was given rituximab, but her thrombocytopenia did not improve. Reexamination of the bone marrow showed a normocellular bone marrow that lacked megakaryocytes, suggesting a diagnosis of acquired amegakaryocytic thrombocytopenic purpura (AATP). To avoid embolic complications caused by eltrombopag, she was treated with cyclosporine, which resulted in her no longer needing platelet transfusions and being able to receive ambulatory treatment instead. We report a case of cyclic AATP in a patient with APS that was successfully treated with cyclosporine.

Keywords

Anti-phospholipid antibody syndrome, Cyclic thrombocytopenia, Acquired amegakaryocytic thrombocytopenic purpura

Introduction

Acquired amegakaryocytic thrombocytopenic purpura (AATP) is a rare hematological disorder characterized by marked thrombocytopenia due to a marked reduction in the number of megakaryocytes in the bone marrow [1]. A few cases of AATP have exhibited periodic fluctuations in the number of platelets (ranging from severe thrombocytopenia to a normal but increased platelet count) [2-7]. The exact pathogenesis of AATP is uncertain, but it can occur incidentally or be associated with an underlying disease, such as an infection, autoimmune disease, or hematological malignancy [1,8]. No cases of AATP associated with anti-phospholipid antibody syndrome (APS) have been reported. Here, we report a case of cyclic AATP associated with APS that was successfully treated with cyclosporine.

Case Presentation

A 52-year-old female was admitted to our hospital because of nasal bleeding and purpura and petechiae of the extremities, which had lasted for two months. She had suffered from APS for 28 years and had been taking oral prednisolone (PSL). There was no family history of hematological disease. A physical examination showed bleeding symptoms, but no signs of thrombotic microangiopathy. The patient's laboratory findings showed mild anemia and marked thrombocytopenia, involving a platelet count of 7,000/μL. Her anti-nuclear antibody titer was 80-fold. Tests for anti-cardiolipin antibodies and lupus anticoagulant were positive, but the results were relatively unchanged from previous data. A test for platelet-associated IgG also produced a positive result (Table 1). Bone marrow aspiration revealed a mildly hypocellular bone marrow with no increase in the number of blasts; however, the number of megakaryocytes was markedly decreased. No diseases that can cause thrombocytopenia, such as viral or bacterial infections, unknown autoim-

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Table 1: Laboratory findings on admission.

< Peripheral blood>		<Serum chemistry>		<Bone marrow examination>	
WBC	9610/μL	AST	14 U/L	NCC	78,000/μL
Band	0%	ALT	9 U/L	Megakaryocytes	0/μL
Seg	52.0%	LDH	154 U/L	M/E ratio	14.64
Eos	1.0%	ALP	167	Myeloblasts	1.6%
Bas	0%	CK	52 U/L	Promyeloblasts	0.8%
mon	4.0%	T-Bil	0.6 mg/dL	Myelocytes	20.8%
Lymph	43.0%	TP	6.3 g/dL	Metamyelocytes	18.4%
RBS	350 × 10^4/μL	Alp	3.8 g/dL	Band	21.2%
Hb	11.6 g/μl	Na	142 mEq/L	Segment	16.8%
MCV	96.9 fi	K	3.5 mEq/L	Eosino	2.4%
MCHC	34.20%	Cl	107 mEq/L	Baso	0%
Plt	7000/μL	Ca	8.5 mg/dL	Promono	0%
Ret	15.9%	P	14 U/L	mono	1.2%
IPF	4.6	NBUN	9 U/L	Lymph	10.4%
<Coagulation test>		Cre	0.54 mg/dL	Plasma	0.8%
PT-INR	1.08	CRP	0.26 mg/dL	Er series	2.4%
APTT	29.8 sec.	< Seroimmunology>		Normoblasts	5.6%
FIG	234 mg/dL	IgG	1340 mg/dL	Macrophages	0%
FDP	1.3 mg/mL	IGA	129 mg/dL		
		IgM	95 mg/dL		
		CH50	31 U/mL		
		C3	44 mg/dL		
		C4	12 mg/dL		
		Anintinuclear antibody	80		
		Anti-Cl + β2GPI	12 U/mL		
		Lupus antocoagulant	1.4		
		Antiplatelet antibody	(-)		
		PAIgG	172 ng/10^7 × cells		

mune diseases, or hematological malignancies, were found. The patient was diagnosed with idiopathic thrombocytopenic purpura (ITP), and the dose of PSL was increased to 25 mg, which resulted in her platelet count increasing to 529,000/μL (Figure 1). However, two weeks later the dose of PSL was decreased to 20 mg, and the patient's platelet count fell to 7,000/μL again, and both mild neutropenia and anemia were observed. The dose of PSL was increased to 40 mg, and the patient's platelet count recovered to 706,000/μL, but after the PSL dose was decreased to 35 mg her platelet count reduced to 6,000/μL, and she suffered repeated nasal bleeding. After that, her platelet count repeatedly and rapidly increased and decreased in the range from 2,000/μL to 916,000/μL, and she presented with repeated nasal, oral, and gastrointestinal bleeding. Therefore, she was diagnosed with cyclic thrombocytopenia (CTP); i.e., cyclic increases and reductions in the number of thrombocytes, independent of the dose of PSL. She received repeated platelet transfusions, but they were not effective. As she was considered to have steroid-resistant ITP, she was given rituximab as a second-line therapy, but it did not have any effect.

The patient's bone marrow was re-examined, which showed a hypocellular bone marrow with no megakaryocytes (Figure 2). A bone marrow biopsy revealed a normocellular to hypercellular marrow with no megakaryocytes. Based on these findings, the patient was diagnosed with AATP.

Her medical history included APS, which is a risk factor for thrombosis, and eltrombopag would have increased the risk of thrombosis further; therefore, she was treated with 200 mg cyclosporine daily. Although her platelet count increases and decreases cyclically, the patient no longer requires platelet transfusions and is receiving ambulatory treatment. Her APS has not worsened, and the PSL dose has been gradually decreased to 4 mg every other day. She continues to receive PSL and cyclosporine as an out patient without exhibiting a bleeding tendency.

Discussion

AATP is a rare hematological disorder characterized by marked thrombocytopenia due to a marked reduction in the number of megakaryocytes in the bone marrow [1]. It has

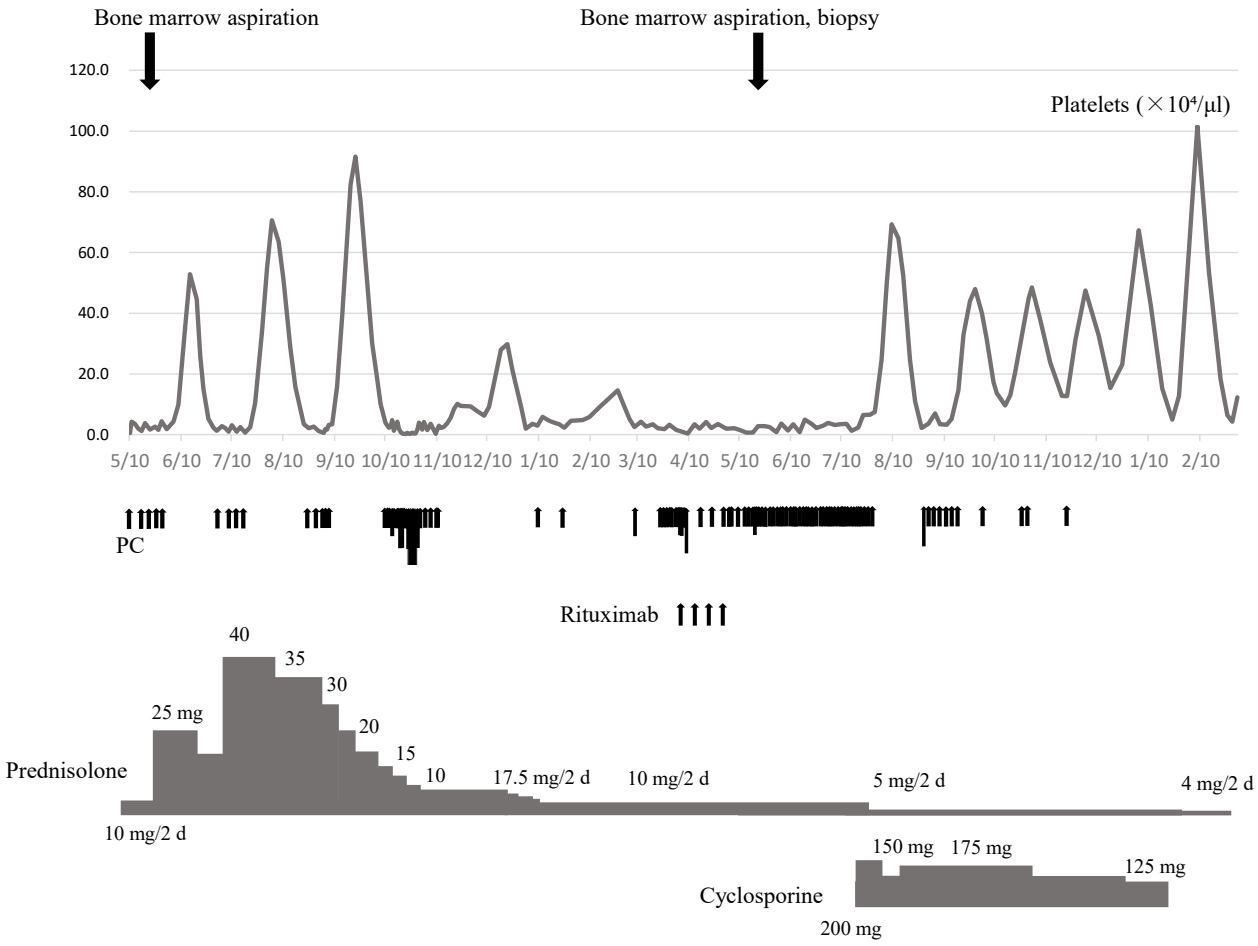

Figure 1: Clinical course.

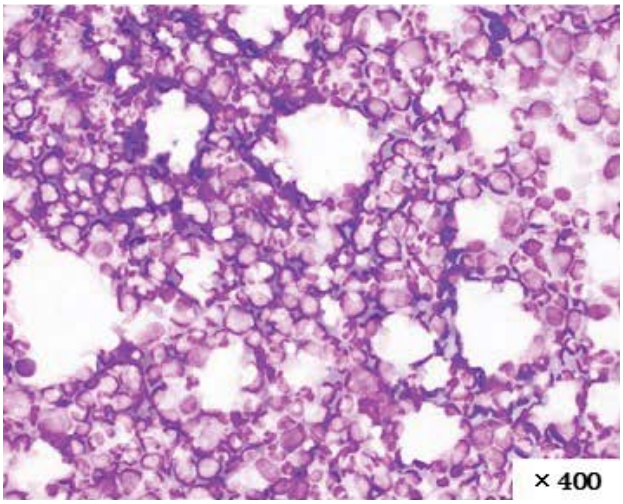

Figure 2: Second bone marrow aspiration (May-Grunwald-Giemsa staining).

The bone marrow aspiration specimen showed a normo-hypercellular bone marrow with granulocytic and erythroid cells, but no megakaryocytes were found.

been reported to occur in patients of all ages. Males account for over half of both patients younger than 30-years-old and those older than 60-years-old, where as females are affected most in the 40-60 years age group [9]. The diagnostic criteria for AATP are as follows: (1) Usually only thrombocytopenia is seen (but slight leukocytopenia and anemia may be present), (2) A reduction in the number of megakaryocytes to < 1/mm^2, and (3) The absence of dysplasia from all cell types. The level of thrombopoietin (TPO), a megakaryocyte-stimulating factor, is usually high in AATP, but this is not a diagnostic necessity [10]. AATP can occur idiopathically or be associated with autoimmune diseases, such as systemic lupus erythematosus (SLE) [10], pure red cell aplasia [11], and autoimmune hemolytic anemia [12]; viral infections, such as cytomegalovirus and parvovirus B19; and certain toxins [3,13]. The exact mechanism responsible for the onset of AATP is uncertain, but dysregulated humoral as well as cell-mediated immunity, consisting of antibodies against TPO and T-cell-mediated destruction of megakaryocytes, has been proposed as a possible pathogenetic mechanism [1,14].

APS is an autoimmune disease. Anti-phospholipid antibodies are also frequently detected in ITP, and an association between ITP and APS has been reported to exist [15-18]. However, no association between AATP and APS has been re-

ported previously. Regarding treatment, intravenous immunoglobulins (IVIG), steroids, cyclophosphamide, and vincristine were not very effective against AATP [1]. As for possible immunological therapies, immunosuppressive drugs, such as cyclosporine, rituximab, and anti-thymocyte globulin (ATG), and allogeneic hematopoietic stem cell transplantation are optional treatments for selected cases [1,12,19]. The response rate of cyclosporine was reported to be about 50%, while that of ATG was 80% [9], but ATG therapy carries a risk of infection and long-term hospitalization. Recently, eltrombopag and romiplostim have been reported to be effective in certain cases [10,20]. Some cases progress to myelodysplastic syndrome, acute myeloid leukemia, or aplastic anemia [21,22].

It is notable that our case involved CTP; i.e., cyclic increases and reductions in thepatient's platelet count. There have been several reports about AATP associated with CTP, and CTP was suggested to be a variant of AATP [2-7]. CTP was reported to cause cyclic suppression of platelet production in terms of the numbers of megakaryocyte progenitors and to suppress the levels of multilineage erythroid and granulocyte/macrophage precursors, which was suggestive of a defect affecting multilineage progenitors [7]. Therefore, AATP and CTP may present with slight leukocytopenia and anemia, as was observed in our case. In some cases, CTP occurs in phase with the menstrual cycle. However, our patient had already experienced the menopause. CTP is usually initially diagnosed and treated as ITP, but steroid treatment, splenectomy, and IVIG treatment are not effective. Although there is no standard therapy for CTP, cyclosporine, mercaptopurine, TPO, and *Helicobacter pylori* eradication may be effective [23]. Furthermore, when CTP occurs in females in phase with the menstrual cycle danazol may be effective because estrogen was reported to influence macrophage functions and hormonal changes during the menstrual cycle, which may affect the production of platelets in cyclic AATP [7].

Although no cases of cyclic AATP associated with APS have been reported, it is not surprising that cyclic AATP occurred in a case of APS, in whichthe anti-phospholipid antibody level also changes cyclically.

One of the differential diagnoses for AATP is thrombocytopenia associated with APS. Thrombocytopenia is frequently found in APS patients (incidence: 22-42%). In such cases, it is usually moderate (> 50,000/μL), does not produce clinical manifestations, and requires no intervention [16]. However, in rare cases (< 1% of APS cases), catastrophic APS (CAPS), involving the development of excessive thrombosis at multiple sites, occurs and leads to multiorgan failure, and the prevalence of thrombocytopenia in CAPS is 65-100% [24]. There is also another condition called APS-related thrombocytopenia [25]. Based on the patient's laboratory data (other than her platelet count), physical findings, and medical history of APS, our case did not meet the criteria for CAPS or APS-related thrombocytopenia. With regard to treatment, APS is a risk factor for thrombosis, and eltrombopag may also increase the risk of thrombosis [26]; therefore, we selected cyclosporine, rather than eltrombopag, in the present case. Fortunately, cyclosporine was effective, and the patient no longer needs platelet transfusions and is receiving ambulatory treatment. Here, we reported a rare case of cyclic AATP associated with APS, which was effectively treated with cyclosporine.

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