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CASE REPORT

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Immune thrombocytopenic purpura associated with rheumatoid arthritis – a report of five cases and review of the literature

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Abstract Immune thrombocytopenic purpura (ITP) associated with rheumatoid arthritis (RA) is relatively rare. We describe five cases of RA with ITP. In all five patients, platelet counts were low, platelet-associated IgG levels were elevated, and bone marrow aspiration showed megakaryocytosis. Glucocorticoid therapy was effective in three cases, but the other two cases required immunosuppressants or intravenous γ-globulin in addition to glucocorticoid. We review the reported cases of RA with ITP and discuss the pathophysiology and differential diagnosis of thrombocytopenia in RA.

Key words Felty's syndrome · Immune thrombocytopenic purpura · Rheumatoid arthritis · Rhupus syndrome

Introduction

Several autoimmune diseases such as Sjögren's syndrome, Hashimoto thyroiditis, and lupoid hepatitis have been described in association with rheumatoid arthritis (RA). In contrast, few cases of ITP, an autoimmune-mediated thrombocytopenia, accompanied by RA have been reported. In this paper, we describe five cases of RA with ITP and review the literature of this rare combination of autoimmune diseases with respect to the pathophysiology and differential diagnosis of thrombocytopenia in RA.

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Case report

Case 1

A 36-year-old man first consulted our outpatient clinic in December 1990 complaining of persistent arthralgia of the bilateral wrists and ankles. He had been diagnosed with RA and was taking lobenzarit (a disease-modifying antirheumatic drug prescribed in Japan) and loxoprofen, prescribed by a local hospital, without improvement. We prescribed D-penicillamine (D-pc), which improved his arthritis. In June 1992, he stopped medication of his own accord. In December 1992, he consulted our hospital again, because of an exacerbation of arthralgia and purpura on the forearms and legs. Laboratory data on admission are shown in Table 1. Thrombocytopenia, megakaryocytosis in the bone marrow, and elevated platelet-associated IgG (PAIgG) established the diagnosis of immune thrombocytopenic purpura (ITP) with RA. The differential diagnoses of our five cases are described in detail in the Discussion. This patient was treated with 60 mg/day oral prednisolone (PSL). His platelet count increased to $9.7 \times 10^4/mm^3$, but started to decrease when PSL was gradually decreased. He was then treated with two courses of 600 mg intravenous cyclophosphamide pulse therapy combined with oral PSL. His platelet count gradually increased, and PSL was decreased successfully.

Case 2

A 73-year-old man with severe gonalgia since 1977 was first seen at our hospital in October 1991. He had been diagnosed with RA and prescribed indomethacin by a local doctor. At our hospital, he was treated with gold sodium thiomalate (GST) from June 1992. In the middle of September 1992, he was admitted to our hospital because of increasing numbers of petechiae and tarry stools. Physical examination revealed active synovitis and petechiae in the extremities. Laboratory data are shown in Table 1. A total of 55 mg GST had been administered prior to admission. All medication including GST, was stopped. Methylpredniso-

Table 1. Clinical and laboratory findings on admission

	Case 1	Case 2	Case 3	Case 4	Case 5
Age/sex	36/M	73/M	74/F	50/F	54/F
WBC (/mm^3)	7100	7000	10100	5000	4700
RBC ($\times 10^4$/mm^3)	525	313	455	400	431
Platelets (/mm^3)	5000	8000	4.4×10^4	8.2×10^4	3.7×10^4
CRP (mg/dl)	0.5	5.6	0.1	1.5	0.1
ESR (mm/h)	ND	47	14	33	34
PAIgG[a] (ng/10^{7}platelets)	32.2	862.6	40.1	51.6	46.0
RAPA	640	640	160	640	640
ANA	160 (Ho)	40 (Ho)	(−)	80 (Sp)	160 (Ho)
IgG (g/dl)	1.22	1.11	1.21	1.98	1.94
IC(C1q)[b] (μg/ml)	18.0	25.8	(−)	(−)	(−)
CH_{50} (U/ml)	38.5	30.0	29.1	44.0	37.9
Anti-DNA-ab	(−)	(−)	(−)	(−)	(−)
Anti-CLβ_2-GPI complex-ab	(−)	ND	(−)	(−)	(−)
Bone marrow	Megakaryocytosis in all cases				

[a] Normal range 5.0–25.0 ng/10^{7}platelets
[b] Normal range <2.9 μg/ml
RBC, red blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PAIgG, platelet-associated IgG; RAPA, rheumatoid arthritis particle agglutination test; ANA, antinuclear antibody; IgG, immunogloblin G; IC(C1q), immune complex (C1q method); Ho, homogeneous; Sp, speckled

lone (mPSL) pulse therapy (500 mg/day for 3 days), followed by 40 mg oral PSL daily, was not effective. Intravenous γ-globulin (400 mg/kg/day for 5 days) stabilized his platelet count between 20000 and 30000/mm^3. Continuous thrombocytopenia for more than 5 months after the cessation of GST favored the diagnosis of ITP with RA rather than GST-induced autoimmune thrombocytopenia.

Case 3

A 74-year-old woman complaining of arthralgia consulted our hospital in 1985. She had been diagnosed with RA and had taken auranofin until April 1995, when she suffered from chronic renal failure and congestive heart failure, and stopped all her medication except PSL. In April 1996, her platelet count dropped from 25×10^4/mm^3 to 7.9×10^4/mm^3. On admission, physical examination revealed no sign of jaundice, lymphadenopathy, or hepatosplenomegaly. She did show arthritis of the bilateral knees and ankle joints, and bony ankylosis of both wrists. Purpura in the body and extremities were observed. Her complete blood cell counts are shown in Table 1. She was diagnosed as having ITP with RA, and PSL was increased from 3 mg to 30 mg/day. Her platelet count gradually increased and returned to normal.

Case 4

A 50-year-old woman had demonstrated thrombocytopenia in 1985 when she underwent an operation for sinusitis. She was diagnosed with ITP by laboratory tests including bone marrow aspiration, and was prescribed danazol by a local doctor. Danazol was later discontinued because of liver dysfunction. She first visited our hospital in January 1988 with complaints of polyarthralgia. She was diagnosed as having RA and treated with a low dose of methotrexate (MTX) (5 mg/week), which relieved her symptoms. Her platelet count has gradually decreased from 11×10^4/mm^3 to 6×10^4/mm^3 since the beginning of 1993. In August 1994, she was admitted to our hospital to investigate the cause of thrombocytopenia. Her laboratory data are shown in Table 1. Megakaryocytosis in bone marrow aspiration and an increase of reticulated platelets in peripheral blood showed that there had been no bone marrow suppression by MTX. We increased the dose of MTX gradually to 10 mg/week, but her platelet count did not fall below 6×10^4/mm^3, which showed that her thrombocytopenia was not caused by hypersensitivity to MTX. We did not give her any specific treatment for thrombocytopenia because her platelet counts fluctuated between 6×10^4/mm^3 and 10×10^4/mm^3.

Case 5

A 54-year-old woman had developed symptoms of bleeding diathesis when she had her first baby, and was diagnosed with ITP according to her bone marrow aspiration. She had been taking PSL for several years. In 1991, she visited our hospital complaining of polyarthralgia and was diagnosed with RA. Her platelet count was 7.3×10^4/mm^3 on the first visit. She was treated with D-pc and salazosulfapyridine (SASP). Her arthritis was ameliorated, but her platelet count decreased gradually and reached 5.4×10^4/mm^3. She was admitted to our hospital in March 1995. She did not show anemia, jaundice, lymphadenopathy, or hepatosplenomegaly. She had arthritis in her left wrist. Laboratory data on admission are shown in Table 1. She was treated with intravenous mPSL (1 g/day) for 3 days followed by 30 mg oral PSL daily. Her platelet count gradually increased. In the outpatient clinic, she complained of arthral-

gia again when PSL was decreased to 5 mg daily and was then treated with D-pc (200 mg/day, three times a week). Although D-pc was effective, her platelet count decreased again to $2.0 \times 10^4/mm^3$ after 11 months. Elevated PAIgG, megakaryocytosis in bone marrow aspiration, and a chronological relationship with the administration of D-pc established the diagnosis of drug-induced autoimmune thrombocytopenia. D-pc was discontinued, and she was treated with 100 mg danazol every other day. Her platelet count increased to $16.6 \times 10^4/mm^3$ and then stabilized.

Discussion

RA is a chronic inflammatory disease, rarely accompanied by thrombocytopenia. Major differential diagnoses for thrombocytopenia with RA include RA + ITP, RA + systemic lupus erythematosus (SLE), Felty's syndrome, and RA with drug-induced thrombocytopenia.

ITP is defined by a low platelet count, increased megakaryocytes in bone marrow, and the absence of other causes of thrombocytopenia. In ITP, autoantibodies bind to platelet membrane surface antigens such as glycoprotein IIb/IIIa, glycoprotein Ib/V/IX, and glycoprotein Ia/IIa[1]; antibody-coated platelets are rapidly cleared by mononuclear phagocytes in the liver and spleen, resulting in a shortened life span. It has been shown that antibodies against glycoproteins on platelet membranes are more specific for ITP than conventional PAIgG. However, accurate methods for measuring these antibodies have only recently been established[2] and are not yet commercially available. Therefore, we used PAIgG to demonstrate the autoimmune-mediated mechanism of thrombocytopenia in our patients.

To our knowledge, 13 cases of ITP associated with RA in Japan, including our five cases, and only three cases from abroad have been reported[3–9] (Tables 1 and 2). Age, sex, disease duration, and stage of RA were diverse. In five patients, ITP was diagnosed before the onset of RA, while in ten patients RA was diagnosed first. In only one patient, were RA and ITP diagnosed simultaneously. Rheumatoid arthritis particle agglutination test (RAPA) was positive in all patients, and antinuclear antibody (ANA) was positive in 11 of 16 patients (69%). Seven (44%) and five (31%) of 16 patients had hyper-γ-globulinemia and increased serum levels of immune complex, respectively. In ITP associated with RA, 6 of 16 patients (38%) were treated with immunosuppressants, intravenous γ-globulin, and/or androgenic steroid in addition to glucocorticoid. Although the number of cases is small, ITP associated with RA might be more refractory to glucocorticoid than ITP alone, since 75%–80% of patients with conventional ITP respond to glucocorticoid therapy.

Patients with SLE show various degrees of thrombocytopenia. Overlapping occurrences of RA + SLE, called Rhupus syndrome, should be considered when a RA patient exhibits thrombocytopenia, although such a combination is relatively rare. Panush et al.[10] reported that Rhupus syndrome occurs in 0.09% of RA cases, and thrombocytopenia is observed in 33% of these patients. In our five cases, all but case 3 were positive for ANA, but anti-dsDNA antibody tests were negative, and serum complement levels were normal. Furthermore, no cases exhibited other clinical features of SLE such as butterfly rash, hair loss, serositis, or renal dysfunction, suggesting that the presence of SLE is unlikely.

Thrombocytopenia is also observed in patients with antiphospholipid antibody (aPL) syndrome (APS). It oc-

Table 2. Reported cases of ITP associated with RA

Author (year)	Age/sex	Stage[a]	Order of disease onset[b]	RAPA	ANA	IgG (g/dl)	IC[c] (μg/ml)	CH50 (U/ml)	Treatment
Saito (1971)	45/F	I	B	(++)	(+)	2.38[d]	ND	23.2	Paramesone 9 mg/day
Nakagawa (1972)	57/F	II	B	(++)	(−)	3.55[d]	ND	43.0	PSL[e]
Misumi et al. (1988)[3]	61/F	IV	C	×320	(−)	1.62	(−)	69.7	PSL 60 mg/day Azathioprine, IVIG[f] Danazol, splenectomy
Sugimoto et al. (1988)[4]	42/F	IV	A (5 years)	×160	×20	2.82[d]	(−)	35.0	PSL 80 mg/day
Kazama et al. (1988)[5]	75/F	IV	A (8 years)	×1280	(−)	0.38	(−)	52.0	IVIG, PSL 40 mg/day
Dasguputa and Grahame (1989)[6]	48/F	ND	A (Many years)	(+)	×10	Normal	ND	Normal	PSL 40 mg/day Danazol 200 mg/2 days
Yamada and Kuroe (1991)[7]	37/F	II	B	×80	×2560	3.43	(+)	Normal	PSL 15 mg/day
Okada (1991)	68/M	IV	A (5 years)	(+)	(+)	ND	ND	Normal	PSL[e]
Kuroki et al. (1993)[8]	55/M	IV	A (10 years)	×1280	(−)	ND	(+)	ND	Cyclophosphamide 300 mg Pulse, IVIG
Sheehan and Stanton-King (1993)[9]	30/F	ND	A (3 years)	×5120	×160	4.0	ND	ND	High-dose PSL, splenectomy
Koriyama (1995)	80/M	III	A (5 years)	×5120	×160	ND	(+)	ND	PSL 40 mg/day

[a] By Steinbrocker's method
[b] A, ITP was diagnosed ahead of RA; B, RA was diagnosed ahead of ITP; C, RA were ITP was diagnosed simultaneously. Disease duration of RA at the onset of ITP is shown in parentheses
[c] Immune complex by the C1q method
[d] γ-globulin
[e] Unknown doses of PSL
[f] Intravenous γ-globulin

curs in nearly 40% of patients with APS. In our five cases, not only anticardiolipin β2GPI antibodies, but also lupus anticoaglant, IgG anticardiolipin antibodies, IgM anticardiolipin antibodies, and IgA anticardiolipin antibodies were negative. Moreover, no cases had a history of thrombosis, miscarriage, or premature delivery.

Felty's syndrome is characterized by chronic arthritis, splenomegaly, and leukopenia. This syndrome occurs in less than 1% of all RA patients and is most common in 50–70-year-old females. Forty percent of patients with Felty's syndrome present thrombocytopenia, but this is seldom accompanied by hemorrhagic complications. Since none of our patients exhibited splenomegaly or leukocytopenia, a diagnosis of Felty's syndrome was ruled out.

DMARDs or nonsteroidal anti-inflammatory drugs (NSAIDs) can induce thrombocytopenia in RA either by inhibiting the production of megakaryocytes in bone marrow, or by immunological depletion of platelets. The latter is called drug-induced autoimmune thrombocytopenia. In drug-induced autoimmune thrombocytopenia, antibodies are produced against drugs which complex with serum proteins. The platelets are bound by the antigen–antibody complex via their Fc receptors, which activates the complement system, causing platelet damage and shortening the life span. In some cases it is difficult to distinguish drug-induced autoimmune thrombocytopenia from ITP because both diseases may present positive PAIgG and/or megakaryocytosis in bone marrow. Therefore, to diagnose drug-induced autoimmune thrombocytopenia, the chronological relationship between the administration of drugs and the platelet count is important. The best proof of drug-induced autoimmune thrombocytopenia may be a prompt increase in the platelet count when a suspected drug is discontinued. However, thrombocytopenia occasionally continues even after the discontinuation of the drug.

Thrombocytopenia caused by gold sodium thiomalate (GST), D-pc, sulfasalazine (SASP), or methotrexate (MTX) has been described in the literature. Thrombocytopenia occurs in 1%–3% of the patients who are treated with GST, but the precise mechanism of this complication has not been determined. It has been reported that IgG can bind to the platelet surfaces in the presence of GST, and that intramuscular administration of GST induced autoantibodies against platelets, leading to thrombocytopenia. Most patients with gold-induced thrombocytopenia have been reported to have HLA-DR3,[11] suggesting the involvement of an immunologenetic mechanism.

Thrombocytopenia is observed in 0.7%–21% of patients prescribed D-pc. Thomas et al.[12] reported that there was a substantial decrease in the production rate of platelets in

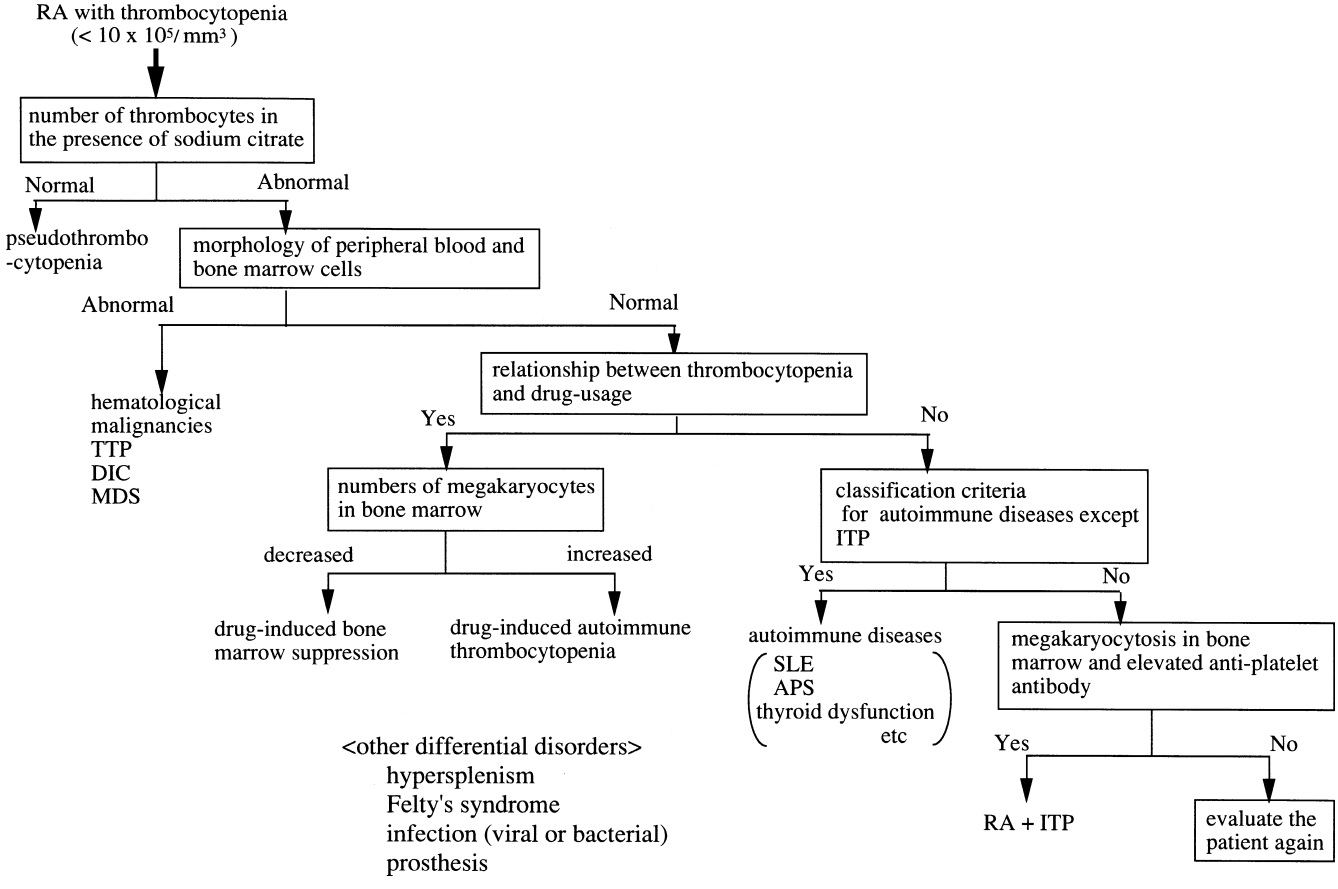

Fig. 1. Flow chart for the differential diagnosis of rheumatoid arthritis (*RA*) with thrombocytopenia. See discussion for details. *TTP*, thrombotic thrombocytopenic purpura; DIC, disseminated intravascular dissemination; MDS, myelodysplastic syndrome; ITP, immune thrombocytopenic purpura; SLE, systemic lupus erythematosus; APS, antiphospholipid antibody syndrome

patients on D-pc, indicating that D-pc may directly inhibit hematopoiesis in bone marrow. However, a case of systemic sclerosis with D-pc-induced autoimmune thrombocytopenia has also been reported. The thrombocytopenia in case 5 of this study seemed to be associated with this mechanism.

Farr et al.[13] examined 300 cases of RA in combination with SASP and found thrombocytopenia in 0.3% of patients. In a retrospective study of RA patients treated with MTX, thrombocytopenia was observed in about 4% of patients. The interaction between MTX and other drugs, such as NSAIDs, might be responsible for its toxicity on bone marrow.[14]

We have devised a flow chart for the differential diagnosis of RA with thrombocytopenia (Fig. 1). We should first exclude pseudothrombocytopenia by examining platelet counts in the presence of another anticoagulant such as sodium citrate. We next examine the morphology of peripheral blood and bone marrow cells to exclude hematological disorders such as thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, myelodysplastic syndrome, and hematological malignancies. We should also investigate the relationship between drug-use and thrombocytopenia. If drug-induced thrombocytopenia can be ruled out, we should ask whether the patient meets the classification criteria for autoimmune diseases except ITP. If all these diagnoses have been ruled out, and the patient meets the diagnostic criteria for ITP, we can diagnose the patient as having RA + ITP. All our cases, except case 5, were diagnosed with RA + ITP according to this flow chart. As described above, case 5 had been diagnosed with RA + ITP, but she developed drug-induced thrombocytopenia during her clinical course.

RA is a chronic inflammatory disease with humoral and cellular immune dysfunctions which are brought about by autoimmune mechanisms. In RA, hyper-γ-globulinemia and autoantibodies, such as rheumatoid factor, are frequently observed. In ITP, autoantibodies against the surface molecules of platelets are responsible for their shortened life span. A disruption of immune tolerance to platelet-surface proteins by some mechanism in RA patients may lead to autoantibody production against the surface molecules and the development of ITP.

In conclusion, although thrombocytopenia is a rare complication in RA, the differential diagnosis for thrombocytopenia includes various disorders and requires a detailed history of illnesses, a physical examination, and laboratory data. A literature review revealed that ITP associated with RA might be more refractory to corticosteroid than ITP alone. Since most of the reported cases of ITP associated with RA are Japanese, a possible genetic relevance for the development of this rare combination of the autoimmune diseases should be investigated.

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