Thrombocytopenia in idiopathic inflammatory myopathies: a case series analysis

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Abstract

Idiopathic inflammatory myopathies (IIMs) are a group of rare connective tissue diseases (CTDs) deeply affecting patients' prognosis. Extra-muscular involvement is not rare and skin, joints and lung are the most common targets. However, also dyserythropoiesis has been described, carrying relevant issues on patients' management and follow-up, as for example, lymphopenia has been associated with an increased risk of rapid progressive interstitial lung disease in anti-MDA5 positive dermatomyositis. Conversely to systemic lupus erythematosus, thrombocytopenia has only been rarely described in IIMs and very few authors have focused on its potential prognostic implications.

We describe five cases of thrombocytopenia in IIMs patients positive for myositis specific (MSA) or associated (MAA) autoantibodies. These reports extend the spectrum of haematological features associated to IIMs, focusing also on potential risk factors for thrombocytopenia occurrence.

Key words

thrombocytopenia, idiopathic inflammatory myopathies, myositis specific antibodies, myositis-associated antibodies

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Introduction

Idiopathic inflammatory myopathies (IIM) encompass a large spectrum of conditions, frequently associated with peculiar autoantibodies that define the clinical spectrum time course of the underlying disease (1-4). Muscle and skin involvement are typical, but also joint and lung manifestations are quite common and the latter frequently represents the main IIM prognostic factor (5, 6). Dyserythropoiesis is not a rare phenomenon in these patients (7-14) and lymphopenia has been associated with the occurrence of rapid progressive interstitial lung disease (RP-ILD) in anti-melanoma differentiation-associated gene 5 (MDA5) positive amyopathic dermatomyositis (DM) (9, 14-16). Until now, only few papers described the occurrence of thrombocytopenia in IIM, as outcome of an underlying thrombotic microangiopathy (17-21), or as autoimmune process (12) or as a drug-related adverse event (13).

In this paper we report five cases of thrombocytopenia occurring in IIM patients positive for myositis-specific (MSA) or myositis-associated autoantibodies (MAA). This association extends the spectrum of IIM features, confirming the heterogeneity of these autoimmune diseases.

Case series

Case 1. A 69-year-old non-smoking Caucasian woman was diagnosed with anti-MDA5 (*EUROLINE, Autoimmune Inflammatory Myopathies 16 Ag; EUROIMMUN*) amyopathic DM in November 2017 because of typical cutaneous lesions, together with arthritis and non-specific interstitial pneumonia (NSIP) pattern at lung high resolution computed tomography (HRCT). Laboratory tests showed antinuclear antibody (ANA) negativity (Indirect Immunofluorescence, IIF), thrombocytopenia (17.000/mmc) without bleeding manifestations, lymphopenia (1.000/mmc) and hyperferritinaemia (824 ng/ml; reference value 18-440 ng/ml), whereas creatine-kinase (CK) levels were not increased (132 mU/ml; reference value 24–167 mU/ml). Peripheral blood smear and bone marrow biopsy were normal, whereas anti-platelet (PLT) antibodies [anti-glycoprotein (GP) Ia/IIa] (*Capture solid phase technology; IM-MUCOR*) were positive. Direct/indirect Coombs test results were not available. Of note, previous PLT count was normal (218.00/mmc). Prednisone (PDN) 40 mg/day was started, but a normalisation of PLT count was achieved following transient corticosteroid increase to 250 mg/day for 3 days and then fast tapering to 12.5 mg/day. Cyclosporine (Cys) 3 mg/kg/day was added as adjuvant immunosuppressive treatment also in light of lung, joint and skin involvement.

After 3 months Cys was discontinued because of hypertensive heart failure. Two weeks later, PLT count decreased from 254,000/mmc to 46,000/mmc. PDN dosage was increased from 12.5 to 50 mg/day and PLT count normalised (212,000/mmc). The patient unfortunately developed Pneumocystis jiroveci pneumonia and trimethoprim/sulfamethoxazole (TMS) was started. Thrombocytopenia relapsed (18,000/mmc) together with the occurrence of skin petechiae. Intravenous immunoglobulins (IVIg, 2 g/kg in 5 days) were ineffective and PLT increased only after TMS withdrawal. Amikacin first and then linezolid were started as treatment of pulmonary infection with a good response. Currently, the patient is on mycophenolate mofetil (MMF) 2 g/day and on to PDN 12.5 mg/day, with normal PLT count and good global disease control.

Case 2. A 18-year-old non-smoking Caucasian woman was diagnosed with DM in December 2017, because of proximal asthenia, typical cutaneous lesions, CK increase (14,000 mU/ml), consistent findings at electromyography (EMG) and muscle biopsy. No joints or lung involvement was observed from the clinical and instrumental point of view. PLT count was normal (258,000/mmc). PDN 50 mg/day was started, and then soon after increased because of dysphagia appearance (methylprednisolone 1 g/day for 3 days IV, then tapering to PDN 75 mg/day P.O.). Subcutaneous methotrexate (MTX), 15 mg/week, was also added to treatment. Few weeks later, because of fever (up to 38°C) and asthenia worsening, she was hospitalised in a Rheumatology Unit. No

infections were found and blood tests revealed a slight increase of CK (313 mU/ml) and ferritin (660 ng/ml), ANA (IIF), titre 1:160, pattern speckled, and anti-NXP2 autoantibodies positivity, while her platelet count was again in normal range (283,000/mmc). IVIg (2 g/kg in 5 days) was started with clinical and laboratory improvement. Because of Pneumocystis jirovecii pneumonia, TMS treatment was started. After one week, the patient developed thrombocytopenia (57.000/ul) and antibodies anti-GP Ia/IIa and anti-GP Ib/IX were detected. Direct/indirect Coombs test results were not available. Peripheral blood smear was normal, whereas bone marrow biopsy was not performed. IVIg re-treatment was performed again for 5 days, for both muscle involvement (2nd monthly course) and thrombocytopenia. While myositis improved again, PLT count did not change (PLT 54.000/mmc). TMS was stopped, and atovaquone started, with subsequent PLT count normalisation. Currently, the disease is well controlled, the patient is on azathioprine (AZA) (100 mg/day) and PDN (12.5 mg/day), whereas IVIg was stopped after 4 other monthly courses.

Case 3. A 51-year-old non-smoking Caucasian woman was diagnosed with DM in February 2018, because of proximal hyposthenia and typical cutaneous findings. Disease was complicated by concomitant mild lung (NSIP aspects at lung HRCT) and joint involvement. At that time, a slight increase of CK (350 mu/ml) and ferritin (541 ng/ml) was observed, whereas platelet count was within the normal range (285,000/mmc). ANA test was positive with a cytoplasmic pattern (1/160) and also anti-MDA5 autoantibodies were positive. PDN (40 mg/day with subsequent tapering until 25 mg/day) and hydroxycloroquine (400 mg/day) were started. She was hospitalised in a Rheumatology Unit in June 2018 because of global clinical worsening (skin, joints and muscle). CK levels were increased until 1000 mU/ml and muscle biopsy evidenced perifascicular atrophy. Laboratory tests showed thrombocytopenia (PLT 68,000/mmc) with negative anti-platelets antibodies (ELISA) and direct/indirect Coombs test. Peripheral blood smear analysis was normal and bone marrow biopsy not performed. AZA 100 mg/day was started. In September 2018, DM was in good global control, also with normal platelet count (PLT 160.000/mmc). PDN was tapered until 12.5 mg/day. During the follow-up, immunosuppressive treatment was changed for arthritis relapses (Cys, tofacitinib, MTX), whereas PLT count was still within the normal range.

Case 4. A 75-year-old non-smoking Caucasian woman, suffering from primary biliary cirrhosis (PBC) with advanced liver disease at biopsy, and complaining for diffuse myalgias was admitted in Intensive Care Unit (ICU). Laboratory tests showed elevated CK (3,301 mU/ml), ALT (151 IU/L; reference value 11–39 IU/L) and AST (289 UI/L; reference value 11–34 IU/L), mild hyperferritinaemia (475 ng/ml), leukopenia (2,440/mmc) with lymphopenia (580/mmc) and thrombocytopenia (30,000/mmc) without haemorrhagic diathesis. Of note, previous laboratory tests showed persistently normal CK (85–120 IU/ml) and PLT (185,000–240,000/mmc) together with doubled transaminases levels (ALT range 50–65 IU/L and AST 55–68 IU/ml). In ICU, clinical examination showed bibasilar lung crackles, marked hepatomegaly with ascitic effusion, muscle weakness and violaceous rash with telangiectasias on her scalp. EMG revealed a myogenic pattern, ANA test (IIF) was positive (1:320 nucleolar pattern) together with anti-Pm/Scl 100, anti-Ro52 and anti-mitochondrial (AMA) M2 antibodies. PDN 50 mg/day was started with a slight CK reduction (645 mU/ml), but worsening of platelet count (17.000/mmc), leading to daily platelet transfusion because of concurrent petechiae. Direct/indirect Coombs test was negative, meanwhile anti-platelet autoantibodies against GP-Ia/IIa were positive. Peripheral blood smear analysis was negative, whereas bone marrow biopsy was not performed. One months later, while the patient was again on 50 mg/day of prednisone, disease course was complicated by Klebsiella pneumonia sepsis, leading to the patient's death. No infections were previously evidenced. Platelet count did not increase along the entire follow-up period.

Case 5. A 66-year-old non-smoking Caucasian woman was diagnosed with anti-MDA5 and anti-Ro52 antibodies positive amyopathic DM in January 2019, because of the occurrence of typical cutaneous lesions. Soon after the onset, the patient presented RP-ILD, leading to ICU admission. Laboratory tests showed mild thrombocytopenia (87,000/mmc; previous values: 234,000) with negative anti-PLT antibodies and normal peripheral blood smear test. A bone marrow biopsy was not performed. CK levels were within the normal range and ANA test (IIF) was negative. Three methylprednisolone courses (500 mg IV) were administered, with subsequent tapering to 1 mg/kg/day IV. PLT count increased (137,000/mmc). For RP-ILD refractoriness, IV cyclophosphamide first (500 mg every 2 week for a total of 2 infusions) and then rituximab (375 mg/m^2 weekly for 4 weeks) were infused, with only transient clinical improvement. In a few weeks, the patient experienced a RP-ILD flare, concomitantly to a further decrease of platelet count (48,000/mmc). The patient died soon after.

Discussion

Thrombocytopenia is an established complication of CTDs such as systemic lupus erythematosus (SLE) (22, 23). In these patients, platelets destruction is generally mediated by antiplatelet glycoprotein IIb/IIIa and anti-glycoprotein Ib/IX antibodies (20), although also non-autoimmune mechanisms may be possible (24). So far, data on the association between IIM and thrombocytopenia are poor and limited to single case reports (8, 25, 26).

We described a series of five cases of thrombocytopenia (27) occurring in patients affected by MSA/MAA positive IIM. Anti-MDA5 antibodies were observed in 3 cases, where the 2 remaining patients were one each positive for anti-NXP2, and anti-Pm/Scl 100 autoantibodies. In our patients, the temporal relationship between

Table I. Description of autoimmune profile, myositis subset, clinical and biological features of thrombocytopenia and global outcome of our case series and review of the literature on IIM patients presenting with thrombocytopenia.

	Sex	Age at IIM onset (years)	Age at thrombocytopenia onset	Myositis specific/ associated antibody	Other positive autoimmune tests	Diagnosis (visceral involvement)	Lower platelet count/mmc	Heamorrages signs	Thrombocytopenia relapses	Inducing/ precipitating factors	Anti-platelet antibodies	Outcome
Patient 1	Female	69	69 years	anti-MDA5	ANA (1/80)	Amyopathic dermatomyositis (skin, joints, lung)	17000	skin petechiae	yes	TMS (2nd episode)	anti-glycoprotein (GP) Ia/IIa	Alive, normal PLT count, joint and lung disease control
Patient 2	Female	18	18 years	anti-NXP2	ANA (1/160, speckled)	Dermatomyositis (muscle, skin)	57000	haemoptysis	0	TMS (1st episode)	anti-GP Ia/IIa and anti-GP Ib/IX	Alive, normal PLT count, muscle disease control, no dysphagia
Patient 3	Male	51	51 years	anti-MDA5	Cytoplasmic positivity of ANA (1/160)	Dermatomyositis (muscle, skin, lung, arthritis)	68000	no	0	no	negative	Alive, normal PLT count, stable ILD, multiple arthritis flares
Patient 4	Female	75	75 years	anti-Pm/Scl and anti-Ro52	ANA (1/320, nucleolar pattern)	Dermatomyositis (muscle, skin, lung)	17000	skin petechiae	0	no	anti-GP Ia/IIa	Dead for septic shock
Patient 5	Female	66	66 years	anti-MDA5 and anti-Ro52	-	Amyopathic dermatomyositis (skin, lung)	48000	no	yes	no	negative	Dead for RP-ILD
Hay *et al*., 1990 [7]	Female	77	77 years	-	direct Coombs test	Dermatomyositis (muscle, skin, lung)	25000	purpuric rash	0	no	positive, not specified	Alive at 3 years follow-up
Kobayashi *et al*., 2000 [23]	Male	14	14 years	-	Platelet-associated IgG	Juvenile Dermatomyositis (muscle, skin, arthritis, lung)	7000	epistaxis and skin petechiae	0	no	positive IgG	Not specified
Ogimi *et al*., 2012 [24]	Female	4	6 years	anti-Jo1	ANA (1/640, speckled pattern) and platelet-associated IgG	Juvenile Dermatomyositis (muscle, skin, arthritis, lung)	2000	skin petechiae	0	no	positive IgG	Alive for 2 years, then lost to follow-up

TMS: trimethoprim/sulfametoxazole; IIM: idiopathic inflammatory myopathies; PLT: platelet; RP-ILD: rapid progressive interstitial lung disease.

thrombocytopenia and IIM was generally very strong. Interestingly, in patient number 4, both manifestations (muscle and PLT involvement) were treatment refractory, while patient number 5 had a concomitant relapse of both RP-ILD and thrombocytopenia, thus strengthening the relationship between IIM and thrombocytopenia. In one case (patient 2), TMS seemed to be the only cause of thrombocytopenia, but we cannot exclude a positivity of anti-PLT antibodies before TMS therapy, as we observed in patient 1.

Regarding the literature data, thrombocytopenia was reported in a patient with juvenile DM (JDM), together with a significant phagocytosis of platelet by macrophages inside a bone marrow with normal cellularity. Although this finding is commonly observed in haemophagocytic lymphohistiocytosis (HLH), the patient had no other systemic or laboratory findings of HLH but platelets-associated IgG were detected, suggesting the presence of platelet-specific antibodies (25), and thus a potential double mechanisms leading to thrombocytopenia. In another case of anti-Jo1 antibodies positive JDM complicated by severe thrombocytopenia (26), serum platelets-associated IgG were detected, whereas bone marrow showed only hypercellularity. Evans' syndrome was suggested in a 77-year-old DM woman with a large number of megakariocytes at bone marrow biopsy and an active consumption of platelets by autoantibodies associated to a positive Coombs test (8). Of note, in our series, bone marrow biopsy was performed only in one case (patient 1) and it was normal. Unfortunately, in none of the prior cases the specific determination of serum circulating anti-PLT antibodies was available, thus not allowing a comparison with our series.

Our cases seem to suggest that autoimmune thrombocytopenia may occur in IIM, and that the use of drugs such as TMS may trigger thrombocytopenia occurrence or relapse (Table I). This latter aspect is particularly intriguing, also because TMS is frequently used as a prophylaxis for Pneumocystis jirovecii in immunosuppressed patients (28). In the case of drug-induced immune thrombocytopenia (DIIT), some antibodies derive from pre-existing antibodies whose reactivity to platelets is weak until the drug is absent, with a significant enhancement through bridging interactions between antibody-drug-glycoprotein on the platelets surface (29). As in the majority of our cases, the epitopes that these autoantibodies usually bound are GP-IIb/IIIa and the GP-Ib/V/IX complex (30), and thrombocytopenia usually recover after 5–7 days from drug discontinuation.

Furthermore, Fontana *et al*. (10) reported three ILD patients with idiopathic thrombocytopenic purpura (ITP). It is established that ILD is one of the major clinical manifestations of IIM (31-34), and interferon-alpha (IFN-α) could be

a possible link between ILD, myositis and thrombocytopenia (35, 36). High levels of IFN-α induce maturation and activation of monocytes and dendritic cells, which express BAFF (5), detected at elevated levels in patients with IIM and ILD (37, 38) and, moreover, in pulmonary specimens of patients with CTDs-related ILD (39). Likewise, high plasmatic levels of INF-α were found in patients with ITP compared to healthy donors (9, 10). In addition, hyperferritinaemia, which is often associated to ILD in patients with DM, is explained by an aberrant activation of the macrophage system, producing high plasma levels of INF-α (5). Four of our patients had hyperferritinaemia at the diagnosis, and all but one had ILD.

In conclusion, we showed that also thrombocytopenia may complicate the course of IIM patients, in particular if positive for MSA/MAA. Searching for anti-platelets antibodies is not included in key recommendations for good clinical practice at IIM diagnosis (40), but we recommend at least a careful monitoring of the platelet count, in particular when IIM patients are treated with TMS.

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