

## Severe Thrombocytopenia in Patient with Dermatomyositis

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**ABSTRACT:** Dermatomyositis (DM) is part of a heterogeneous group of systemic diseases called idiopathic inflammatory myopathies. As in other autoimmune connective tissue diseases (CTD), abnormalities of hematopoietic tissue and/or peripheral blood cells may develop and represent an important prognostic factor. Most common CTD associated with thrombocytopenia (TP) are systemic lupus erythematosus and antiphospholipid syndrome. DM-related TP is less frequent and may develop in the context of an underlying malignancy. Severe TP related to myositis is a very rare occurrence. We report a case of a male patient diagnosed with acute DM, debilitating muscle weakness and rapid development of severe TP.

**KEYWORDS:** dermatomyositis, thrombocytopenia, idiopathic inflammatory myopathies.

### Introduction

Dermatomyositis (DM) is part of a heterogeneous group of systemic diseases called idiopathic inflammatory myopathies (IIM). The main types of IIM are DM, polymyositis, inclusion body myositis and necrotizing autoimmune myopathy [1]. Common features of IIM are muscle weakness, raised muscle enzymes and presence of various patterns of inflammatory infiltrate inside or adjacent to the skeletal muscle fibers [2]. Additional skin involvement in DM includes cutaneous features, such as macular erythema of the neck and posterior shoulders, heliotrope rash of the eyelids and Gottron's sign. As in other autoimmune connective tissue diseases (CTD), abnormalities of hematopoietic tissue and/or peripheral blood cells may develop and represent an important prognostic factor and disease activity-marker [3]. Thrombocytopenia (TP) can develop in the course of most CTD, being associated either with antibody-mediated destruction, intravascular platelet consumption or decreased production. Most common CTD associated with IT are systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APL) [4]. IIM-related TP is less frequent and may develop in the context of an underlying malignancy. Severe TP (platelet count <50,000/mm<sup>3</sup>) related to myositis is a very rare occurrence. We report the case of a male patient diagnosed with acute DM, with debilitating muscle weakness and rapid

development of severe TP which worsened even after initiation of glucocorticoid therapy.

### Case report

We present the case of a 63 year-old male patient admitted to the rheumatology department, with severe proximal muscle weakness which rendered the patient bedbound. Other clinical features were dysphagia, periorbital edema, intense erythematous skin rash on the neck and upper thorax (see Fig. 1).

Disease history included only a surgical intervention for duodenal ulcer 20 years prior. Onset of muscle symptoms was approximately one and a half months before admission, with rapid worsening and debilitating weakness. Written informed consent was obtained from the patient prior to being considered in this study.

Initial laboratory work-up revealed mild microcytic anemia-hemoglobin=10.38g/dl, moderate thrombocytopenia-platelets count=91220/mm<sup>3</sup>, increased inflammatory markers-erythrocyte sedimentation rate=82mm/h, C-reactive protein=45.04mg/l, elevated muscle enzymes-glutamic oxaloacetic transaminase (GOT)=813U/l, creatine kinase (CK)=7648U/l, lactate dehydrogenase (LDH)=888U/l. At this point diagnosis of DM was established. Autoimmune panel was negative for myositis-specific antibodies and an extended antinuclear antibody essay was also negative. Electromyography was performed and revealed a mixed myopathy and neuropathy pattern.

Corticosteroid (CS) therapy was initiated starting with a 5-day course of intravenous methylprednisolone (MP) in a dose of 500mg per day, followed by oral 1m/kg/day CS.

After the first two days of CS pulse-therapy, the patient showed promising results, with significant improvement in muscle strength and also considerable fading of the skin rash.

He was no longer bedridden and walked with assistance. Also, the muscle enzymes and inflammatory markers showed decreasing trend.

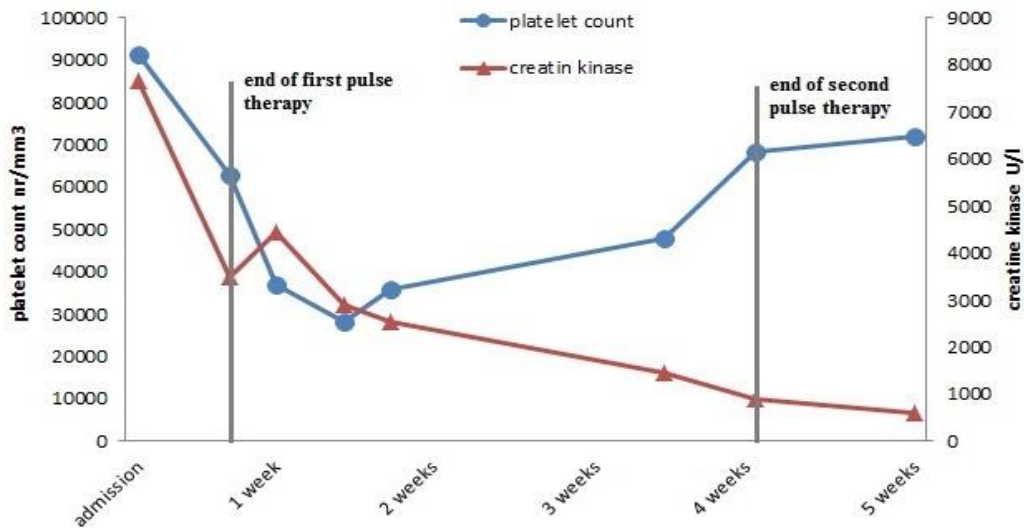
Paradoxically, although a general improvement was evident, repeated blood counts after the course of intravenous CS and during oral CS therapy revealed a continuous decrease in white blood cells (WBC) and platelets.

The patient developed severe TP with platelet count dropping to 28.000/mm<sup>3</sup> in just 10 days despite on-going CS medication (see Fig. 2).

Muscle biopsy was postponed due to severe TP and the patient was referred to the hematologist for further investigations.



**Fig. 1. Clinical features on admission included skin changes such as heliotrope rash of the eyelids and periorbital edema**



**Fig. 2. Dynamic follow-up of platelet count and serum levels of creatin kinase; although enzyme levels have a steady drop, there is an initial lack of response regarding the platelet count, with maintained thrombocytopenia after completion of first pulse therapy; platelets reach a minimum level of 28000/mm<sup>3</sup> after 10 days of corticosteroid treatment; second pulse therapy offers greater benefit concerning both thrombocytopenia and clinical symptoms**

Bone marrow biopsy ruled out a central cause of TP with normal distribution of all cellular lineages. Peripheral smear did not provide significant information. Coagulation tests were normal. Antiplatelet antibodies and viral hepatitis infection markers were screened and yielded negative results. Any prior or present medication associated with secondary TP was ruled out.

Although the patient was scheduled for a follow-up rheumatology visit, he was admitted only after 2 weeks because oral CS medication was taken intermittently at home and eventually interrupted. Muscle weakness relapsed and thus a higher dose of MP 1g/day in pulse-therapy was administered for 5 days, followed again by oral CS 1mg/kg/day. On this second course of CS, the platelet count increased to 72.000/mm<sup>3</sup>, CK and TGO dropped to 582U/l and 107U/l, respectively.

Underlying malignancy screening included various tumor markers for digestive, pulmonary, prostate and liver neoplasm, which were all negative, gastrointestinal (GI) endoscopy and computed tomography (CT). Upper GI endoscopy was normal. CT scan revealed a segmental thickening of the sigmoid colon wall, of up to 28mm, and features of perienteric inflammatory infiltrate. The patient did not report any hemorrhage or changes in bowel habits. Unfortunately, a colonoscopy could not be performed due to inappropriate preparation and subsequent lack of patient-cooperation which postponed the examination for a future admission. The patient remained on a dose of 1mg/kg/day oral CS until further follow-up evaluation.

## **Discussion**

Hematologic abnormalities are frequently encountered in the setting of CTD. A hallmark of every CTD is the autoimmune status coupled with inflammation-associated pathogenesis. This can affect virtually any blood cellular lineage. Chronic immune activation and dysregulation can lead to hematologic malignancies, predominantly lymphoproliferative disorders, in which genetic aberrations cause a clonal proliferative drive. SLE is considered a CTD archetype in regard to the hematologic manifestations, which have also been included in the American College of Rheumatology classification criteria [5].

CTD-associated TP may be induced by immune or non-immune pathways. Non-autoimmune pathogenesis includes ineffective

bone marrow thrombopoiesis, low thrombopoietin levels or peripheral sequestration or consumption. Â

Autoimmune CDT-related TP develops in the presence of cell-specific autoimmunity, positive anti-platelet, antithrombopoietin and antiphospholipid antibodies [3]. Secondary immune thrombocytopenia (ITP) seen in the context of a underlying CTD has a similar pathophysiology to primary ITP, that is peripheral destruction or decreased central production due to antibodies targeting platelets or antithrombopoietin receptor [4].

Studies have demonstrated the affinity of both T and B lymphocytes from ITP patients for specific platelet auto-antigen. In vitro stimulation of T-helper lymphocytes by platelet-CD154 has been proven capable of driving B-cell antibody production [6]. Although initially studies were carried out on platelet-associated IgG, which had 90% sensitivity, but low specificity, the current diagnostic markers for autoimmune TP are the antibodies targeting platelet surface glycoproteins, such as GPIIb-IIIa, GPIa-IIa or GPIb-IX. Using these markers, a specificity of 78-93% is obtained, but with a lower sensitivity of 49-66% [7]. Effect of antibodies capable of megakaryocytopoiesis inhibition has also been detected in plasma of ITP patients [8]. Absence of specific antibodies does not exclude ITP and suggest an alternative destruction mechanism. This is based mainly on the lysis-induced effect of cytotoxic T-lymphocytes, as in one study where ITP patients CD3+/CD8+ lymphocytes produced significant lysis compared to controls and ITP in remission [7]. In ITP, bone marrow biopsy will only reveal an increased number of megakaryocytes without any other abnormality.

Higher occurrence of TP among CTD patients is seen in SLE and APS with prevalence of up to 27% and 29%, respectively (higher in secondary APS) [9,10]. Compared to other CTD, IIM diseases rarely develop moderate or severe TP. Also, occurrence of TP in myositis disease imposes a differentiation between a primary myositis-related TP and an underlying malignancy with hematologic manifestations. In a retrospective study which analyzed 85 patients diagnosed with ITP secondary to various CTDs, DM-ITP accounted for only 2.35% of patients, compared to 38.82% of patients diagnosed with SLE-ITP [11]. Just a few case-studies report the association of autoimmune TP with DM and inclusion body-myositis [12-14].

Development of ITP should also prompt a suspicion of an overlap syndrome, mainly with SLE. The association of IIM and bicytopenia or pancytopenia is a rare occurrence. Evans syndrome, defined as autoimmune hemolytic anemia and TP, has been described in one case of a 77 years-old female patient with subsequent diagnosis of DM [15].

Pancytopenia develops in the context of CDT most frequently in SLE or as a complication in the form of a hemophagocytic syndrome (HPS). Kobayashi et al described a case of juvenile DM which developed a platelet-specific hemophagocytosis detected on bone marrow biopsy [16].

Mechanisms through which HPS can arise include deposition of circulating immune complex to the hematopoietic cells or facilitated macrophage-phagocytosis by cellular-specific antibodies [17].

Specific therapy approaches depend of the underlying etiology of TP. Platelet transfusion may provide an immediate increase in cell count in cases of severe bleeding. It is important to mention that this effect will be minimal in an ITP and should be reserved only for life-threatening situations. First line treatment in ITP is generally a CS agent with or without an initial intravenous pulse therapy. The common starting dose for adults is prednisone 1-2mg/kg per day, with gradual tapering after several weeks. Usually, initial response rates range from 70% to 80%. Second-line therapies for ITP include splenectomy, with very high response rates, and association of other agents such as: intravenous immunoglobulin, azathioprine, cyclophosphamide or cyclosporine [18].

Our case posed numerous difficulties regarding the rapid decrease in platelet count during CS therapy, fast relapse after treatment recommendations were neglected and inability to proper investigate a potential malignant context suspected on CT scan. Also, the additional tests concerning the central and peripheral blood cell distribution or autoimmune status targeting platelets yielded negative results. Rapid decrease in platelet count, while it is proven to be a definite disease activity marker in SLE, it is not commonly attributed to a high disease state in DM, neither a common complication of myositis in general. In our case, intense immune activation and a potential underlying malignancy are two possible mechanisms through which severe TP developed. Under-dosed CS on initiation and improper maintenance of recommended

posology contributed both to the refractory state in the first weeks of treatment. Fortunately, a more aggressive approach provided beneficial results with improvement of both muscular symptoms and platelet count.

## Conclusions

Cases reporting thrombocytopenia as hematologic complication in DM are very limited.

Immune thrombocytopenia is an exclusion diagnosis especially in the absence of platelet-specific antibodies.

Severe forms of thrombocytopenia draw the suspicion of an overlapping connective tissue disease, such as SLE, underlying malignancy or hemophagocytic syndrome and prompt the need for a higher corticosteroid doses before opting for second-line approaches.

Our case showed that acute DM can develop severe and sustained thrombocytopenia.

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