# Diagnosis of Antiphospholid Syndrome Uncovered Co-occurrence of Myelodysplastic Syndrome: A Case Report

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Myelodysplastic syndrome (MDS) is frequently associated with clinical manifestations of autoimmune disorders (AD) and inflammatory responses of the immune system. The biological linkage between MDS clones and the occurrence of autoimmune manifestations is mirrored by the response of the latter to MDS modifying therapeutic approaches [1]. We encountered a rare case of MDS coexisting with antiphospholipid syndrome (APS), which was effectively treated with a hypomethylating agent followed by allogenic bone marrow transplantation.

MDS is a group of clonal myeloid neoplasms characterized by ineffective hematopoiesis and abnormal cellular morphology with variable risk of transformation to acute myeloid leukemia (AML) [1].

Approximately 10–20% of MDS patients present with AD. In those cases, the diagnosis may be challenging [1]. The clinical presentation varies from clinical syndromes to laboratory abnormalities without an overt disease in 22% of patients [2]. To the best of our knowledge no case of APS associated with MDS has been reported.

Several immune cell subsets display diverse functional patterns in MDS patients and cytotoxic T-cells have been advocated in the inhibition of hematopoietic precursors [1].

Management of MDS-related ADs could be troublesome due to underlying risk of cytopenias, infectious complications, and secondary MDS [1].

Last, knowing that AD may respond to MDS-modifying therapeutic approaches strongly highlights potential pathophysiological mechanisms implicated in the disease course [1].

We described a specific presentation of AD and antiphospholipid syndrome (APS), which was diagnosed as an underlying MDS, and discussed the treatment strategy that led to remission of both conditions.

## PATIENT DESCRIPTION

A 70-year-old Caucasian male with a past medical history of prostate malignancy treated with prostatectomy and pelvic radiation 5 years prior presented with burning red lesions on his right hand and foot followed by necrosis of the right fifth toe. He was hemodynamically stable, afebrile, with a reticular hemorrhagic rash was appreciated on the right foot, which then spread as sensitive, livedoid lesions to his right extremities.

Laboratory results showed hemoglobin 13 g/dl, leukopenia 4300 K/microL, lymphopenia 600 K/microL, platelets 210 K/microL, creatinine 1.5 mg/dl, lactate dehydrogenase (LDH) 583 IU/L, C-reactive protein (CRP) 8.0 mg/L, and normal aminotransferases. Clotting panel PT 13.3 seconds (11–13.5 seconds), prolonged APTT 47.6 seconds (30–40 seconds), fibrinogen 488 mg/dl, and an elevated D-dimer 1500 ng/ml.

Peripheral blood smear ruled out the presence of schistocytes, however, dysplastic neutrophils were detected. All three tests for antiphospholipid antibodies (APLA) were positive; Anticardiolipin immunoglobulin G (IgG) 114, IgM 67 (0.0–19.9 U/ml), B2 glycoprotein IgG 107, IgM 133, IgA 50 (0.0–19.9 U/ml), and a borderline lupus anticoagulant (LAC): Russell viper venom time (RVVT) ratio 1.4 (0–1.4).

Further evaluation, including urinalysis, iron storage, thyroid function tests, vitamin B12, folate, serum, and urine immunofixation tests were within the normal range. Infectious disease workup was negative. Studies for autoimmune panel of antinuclear antibody (ANA), antineutrophil cytoplasmic autoantibodies (ANCA), double stranded DNA (dsDNA), anti-centromere, and scl-70 antibodies, haptoglobin, RF, C3 and C4 were all negative.

Flow cytometry of bone marrow aspiration revealed one percent of myeloid blasts, fluorescence in situ hybridization (FISH) was positive in 46% of cells for del7 with the remaining probes negative.

JAK2 V617F was found mutated. Bone marrow biopsy demonstrated a hypocellular marrow (30% cellularity) with granulocytic hyperplasia and trilineage dyspoiesis with 8% myeloblasts present.

Angiography demonstrated lack of distal flow of the left popliteal artery. Echocardiography showed good left ventricular function with no evidence of vegetations.

A toectomy was conducted in addition to multiple skin biopsies with findings compatible with thrombotic angiopathy. A diagnosis of treatment-related myeloproliferative neoplasm (MDS-MPN) secondary to pelvic radiation was established at intermediate-risk (IPSS-R 4) with autoimmune phenomena, most probable APL due to single occasion of laboratory results by Sapporo criteria [3]. Anticoagulation with warfarin was started and aspirin was halted.

Due to worsening of ischemia of the right foot with new livedoid lesions and excruciating pain at therapeutic INR (international normalized ratio) level, laboratory findings of further cytopenia, as well as all three APLA remaining positive 12 weeks apart, aspirin was reintroduced. The patient was treated with 5-azacytidine (a hypomethylating agent) for MDS following by allogenic bone marrow transplantation from an unrelated female donor. Post-transplant, pain and livedoid lesions resolved. Repeated marrow aspirates verified complete remission on FISH and full chimerism of the donor (100% XX).

A year from transplantation, three APLA tests were negative: anti-cardiolipin IgG 3.5, IgM 1.7 (0.0–19.9 U/ml), B2 glycoprotein (0.0–19.9 U/ml), IgA 12.8, IgM 2.3, IgG 1.2; and 1.05 LAC:RVVT ratio (0–1.4). Nevertheless, the patient continued taking warfarin without bleeding episodes or other symptoms.

## COMMENT

The co-occurrence of AD in patients with MDS is widely reported, concomitantly or after MDS diagnosis, most frequently with vasculitis, seronegative polyarthritis, and specific skin lesions. Compared to MDS without vasculitis, these patients are generally younger with a prevalence of male sex [1]. Cases of APLA without a clinically overt disease were reported among 22% of 123 patients with MDS [2].

Other than trisomy 8 in patients with Behçet's disease, which was associated with MDS, no significant association between cytogenetic findings and MDS associated with AD was found [1].

The pathogenesis of MDS-related autoimmune and inflammatory disorders is still undetermined, and the prognostic significance remains controversial considering the complications that may significantly impact on quality of life and affect the timing and type of MDS-directed therapy [1].

Allogeneic hematopoietic stem cell transplantation (HSCT) is currently the only curative modality for 30–80% of patients with MDS, mainly reserved for higher risk patients [1], whereas patients in lower-risk categories are often managed conservatively, based on pyrimidine analogues [1]. These drugs are classified as epigenetic modulators that act through a demethylating mechanism to alter gene regulation and allow differentiation to mature blood cells from the abnormal MDS stem cell. Its immunomodulatory effect reduces disease burden, modifies the expression of neoplasia-related inflammation, and directly affects the AD [1].

HSCT has evolved from an experimental concept to an effective treatment option for severe AD and has a unique ability to restore immune regulation. However, most HSCT procedures in refractory ADs have involved autologous stem cells. Allogeneic HSCT has curative potential based on studies in experimental models of AD, case reports, and a registry analysis but carries significant risks of rejection and graft-versus-host disease [4].

Scarce data regarding mainly primary APS patients with previously positive APLA profile and subsequent become negative have been reported. These studies suggested the possibility of anticoagulation discontinuation in APS patients with low-risk and venous thrombosis with a concomitant lower risk factor after a short follow-up. Studies with more patients and longer follow-up are lacking. Thus, the question to continue warfarin treatment in the absence of APS autoantibodies remains indeed unclear and is considered a research agenda.

A discussion of risks, benefits, and differences in anticoagulant drugs is paramount and must be discussed with the patient. There is limited data regarding individualized management, including patient preference concerning long-term anticoagulation and the risk of recurrent event. These options must be considered against the risk of bleeding, as in our case [5].

## CONCLUSIONS

In patients with hematologic diseases, physicians should be aware of underlying diseases to provide timely intervention. MDS-directed therapy to eradicate accompanied autoimmune disease should be considered.

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