Large Vessel (Takayasu's) Arteritis in a Patient With Myelodysplastic Syndrome: Is There a Common Pathogenesis ?

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Abstract

Autoimmune phenomena may complicate the course of myelodysplastic syndromes (MDS) but large vessel arteritis is a rare event. We report a case of large vessel arteritis in a patient with MDS. A 62-year-old male presented with thrombocytopenia and was diagnosed with low-risk MDS, (< 5% blasts in his bone marrow and a normal karyotype). Shortly thereafter he developed large vessel (Takayasu's) arteritis (TA) that responded well to oral corticosteroid and methotrexate therapy. Ten months later the MDS transformed into acute myeloid leukemia (AML). After a successful induction course with cytarabine and daunorubicin he underwent allogeneic transplantation from a matched unrelated donor with reduced-intensity conditioning. The transplantation was complicated by systemic cytomegalovirus (CMV) disease and he died 6 weeks post transplantation. Takayasu's arteritis is an uncommon form of vasculitis affecting primarily young women and is atypical for elderly males. Though autoimmune manifestations in MDS occur in 10%-18.5% of patients, usually large vessels are spared. In MDS, activated T cells are thought to mediate bone marrow failure via overproduction of proinflamatory cytokines that cause stem cell apoptosis. These T cells may also mediate the autoimmune phenomena in MDS. The prognostic significance of autoimmunity in the course of MDS is not yet determined. Some reports suggest worse prognosis. The case illustrates a possible association between MDS and large vessel vasculitis and suggests a possible relationship between the presence of autoimmune syndromes and the outcome of patients with MDS.

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Introduction

The myelodysplastic syndromes (MDS) encompass a range of disorders in the production and maturation of cells belonging to the myeloid lineage. It is characterized by bone marrow dysplasia, peripheral cytopenias and the potential to progress to acute leukemia. The cytopenias in some forms of MDS may be immune mediated. Activated T cells are presumed to attack and induce apoptosis of myeloid stem cells. In addition, nonhematologic autoimmune phenomena are well known in MDS patients and include arthritis, vasculitis, and connective tissue disorders.[1,2] The vasculitides usually involve small vessels of the skin but may occur in medium size vessels[3] and rarely in large vessels.[4,5] The International Prognostic Scoring System (IPSS) classifies MDS patients into prognostic risk groups.[6] The role of immunologic manifestations in disease assessment of MDS patients has not been determined. We describe a patient with MDS and vasculitis and discuss potential common pathophysiologic mechanisms of both diseases.

Case Report

A 62-year-old Ashkenazi Jew male consulted his general practitioner because of easy bruising. During the previous year he had suffered from furunculosis in the posterior aspect of his left leg, which was treated with local drainage. There was no history of smoking, alcohol, or substance abuse. A complete blood count revealed thrombocytopenia of 65 × 10^9/L, hemoglobin (Hb) of 11.9 g/dL, and white blood cells (WBC) of 4.2 × 10^9/L. Iron,

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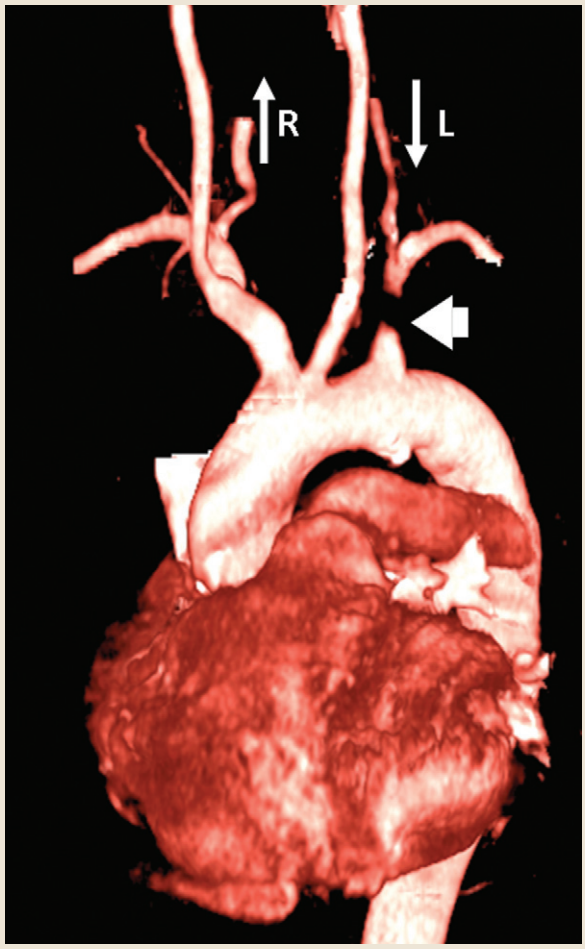
folate, and B_{12} levels were normal. The peripheral blood smear demonstrated thrombocytopenia and Pelger-Huet forms among normal appearing granulocytes. The bone marrow was hypercelluler with decreased number of megakaryocytes and several micromegakaryocytes. The white cells showed a left shift, dysplastic neutrophils, and < 2% blasts. The karyotype was normal (46,XY chromosomes in 20 metaphase cells).

The patient was diagnosed with MDS, RCMD (refractory cytopenia with multilineage dysplasia, 2008 WHO classification) with a low IPSS score. He continued to be followed in the hematology clinic with no specific treatment. Two months later he was hospitalized due to chest pain, transient monocular blindness (amaurosis fugax), fatigue, low-grade fever, night sweats, and weight loss. His physical examination was remarkable for diminished pulses in the left arm and femoral arteries. Fundoscopic examination was normal. The erythrocyte sedimentation rate (ESR) was 96 mm/hour and C-reactive protein was 17.2 mg/dL (normal range, 0-1 mg/dL). The WBC was 4.8 × 10^9/L, the Hb 9.3 g/dL, and platelet count was 67 × 10^9/L. There were no biochemical abnormalities. Liver function tests were normal. HIV serology was negative. Blood cultures were sterile and a transthoracic echocardiogram showed no valvular vegetations. Immunologic studies showed antinuclear antibody of +2 out of +4, anti-DNA of 1.57 µg/mL (normal value 0-1.5), low positive titer for P-ANCA and C-ANCA and elevated polyclonal serum levels of IgM of 381 mg/dL (normal value, 65-280 mg/dL). Computed tomography (CT) angiography and carotid artery Doppler imaging demonstrated complete obliteration of the left subclavian artery and retrograde flow from the left vertebral artery supplying the left axillary artery and hand (Figure 1). Furthermore, additional stenotic lesions were observed in the origins of both carotid arteries, along the aorta, in the femoral and mesenteric arteries. An ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (PET-CT) scan was performed and demonstrated large arteries with active metabolic centers in the vascular walls and not on the intravascular endothelium, suggesting a multifocal arterial inflammatory disease (Figure 2). A temporal artery biopsy was normal. A diagnosis of TA was made and he was treated with prednisone 1 mg/kg. Within weeks, he experienced a marked clinical and laboratory improvement within weeks. The ESR decreased to 12 mm/hr. The platelet count was unchanged. Due to steroid-induced insomnia and hypertension, methotrexate at a dose of 12.5 mg/week was added as a steroid sparing agent. In the following months, he was admitted on 3 separate occasions due to recurrent deep soft tissue staphyloccocal infections that were treated with antibiotics and surgical drainage. The prednisone dose was slowly tapered to 5 mg/day and 12 months after diagnosis of TA there were no signs of active inflammation. The major vessels were normal on a follow-up PET-CT scan. Concurrently, he developed recurrent bruising, accompanied by fatigue, fever, and night sweats. The platelet count dropped to 37 × 10^9/L, hemoglobin was 11.1 g/dL and the WBC was 18 × 10^9/L. A peripheral blood smear showed marked dysplastic left shift in the white series and several blast forms. A bone marrow aspirate was hypercellular with 60% myeloblasts that were positive for CD34, CD33, and CD117 on immunophenotyping. The karyotype was again normal and acute myeloid leukemia (AML) was diagnosed. Induction with cytarabine and daunorubicin was given and the patient achieved complete remission. This was followed by allogeneic bone marrow transplantation from a matched unrelated donor. He received reduced-intensity conditioning with fludarabine, antithymocyte globulin, and busulfan. One month later he developed CMV disease with pneumonitis and respiratory failure. Despite specific antiviral treatment and maximal supportive care he died after 2 weeks.

Figure 1 Volume Rendered CT Images Showing Complete Obliteration of the Left Subclavian Artery at its Origin (Arrow Head)



The distal subclavian artery is supplied by reverse flow from the left vertebral artery. Arrows indicate direction of flow in the vertebral arteries as demonstrated by Doppler (L-left, R-right).

Discussion

The pathophysiology in most types of MDS remains unknown. An accepted model of MDS implicates a pathologic clone of stem cells expressing antigens that trigger the expansion and activation of cytotoxic T cells.[7,8] This activation results in overproduction of cytokines such as TNF-α and IFN-γ that induce apoptosis of normal stem cells causing pancytopenia. This model is supported by the finding of CD34+ apoptotic stem cells in bone marrow samples from patients with MDS[9] as well as by an inverted CD4/CD8 ratio of T cells[10] and of highly cytotoxic T cells that are CD8+, CD28−, CD57+ by immunophenotyping[11] in the periph-