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Case Report

Hyperviscosity Syndrome: An initial manifestation of Rheumatoid Arthritis

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Abstract

This case involves a 41-year-old Hispanic male with a past medical history of hypertension, who presented to the emergency room with a history of dizziness, recurrent syncope, weight loss, hematuria, epistaxis and gingival bleeding for several months. He had an extensive hematology work-up, which included a bone marrow biopsy. It showed a hypercellular bone marrow with mild myelofibrosis but no evidence of malignancy. His serologies showed a significantly elevated rheumatoid factor (RF), significantly elevated anti-Cyclic Citrullinated Peptide IgG antibodies, a negative anti-nuclear antibody & significantly elevated anti-double-stranded antibody levels. Of note, the patient had no synovitis on exam, and no other signs of rheumatoid arthritis (RA).His clinical picture and work-up was consistent with hyper viscosity syndrome with a serum viscosity level of 5.6 cpoise (RR: negative < 1.5 cpoise) .He was successfully treated with three therapeutic sessions of plasma exchange, along with high-dose pulse steroids and Rituximab.

Hyper viscosity syndrome, as a complication of rheumatoid arthritis, has been well described in the literature. It is usually due to a high concentration of RF. In most cases, hyper viscosity syndrome was a complication of longstanding symptomatic RA. While, there are some cases where hyper viscosity syndrome was the presenting manifestation, these cases were most certainly associated with significant synovitis. To our knowledge, this is the first case where hyper viscosity syndrome is the presenting manifestation of rheumatoid arthritis, with no associated synovitis.

Introduction

A 41-year-old Hispanic male, with a past medical history of hypertension and anemia,presented to the Emergency Room (ER) with a several month history of bilateral blurry vision,headaches, bleeding gums,epistaxis, and recurrent syncope,with associated loss of consciousness.

His symptoms began two years prior, when he presented to an outside hospital with bilateral ocular redness, irritation and blurred vision. On exam, in the emergency room, he was found to have bilateral conjunctival injection, and was discharged home. He was well until a work injury six months ago. His labs at that time showed a hemoglobin of 6.5 g/dl (RR:12.7-17.0g/dL), for which he received multiple transfusions. His IgG level was 4962 mg/dl (RR:700-1600 mg/dL), with normal IgM and IgA parameters. The cause of this new anemia was not known at that time.

Since then, the patient reported daily episodes of dizziness and with multiple frequent episodes of syncope with loss of consciousness, lasting 1 minute or so. What was worrisome to him was the frequency of attacks, which increased over the past 3 months, from 5-6 times a month to daily. He reported that these episodes occurred without significant prodrome such as lightheadedness, chest pain, flushing, but he did recall intermittent palpitations before his falls. He did not have any head trauma. His wife, who witnessed these episodes, reported the same series of events.

One month ago, he developed new epistaxis. His labs revealed a hemoglobin of 6.4 g/dl (RR:12.7-17.0g/dL), ferritin of 28.3 ng/mL (RR:30-400mg/mL) and a transferrin saturation of 5.5% (RR:15.5-50%). He again received blood product transfusions and an iron infusion and was discharged to follow up with hematology as outpatient. However, this was not possible because of a lack of insurance.

Before this new admission to our facility, he had noticed pink-colored urine, which had been present for 3 days, along with his other presenting complaints. On physical exam, his initial exam was associated with normal vitals, but the patient appeared tired and lethargic. His ocular exam showed bilateral conjunctival hemorrhages, while his head and neck exam showed diffuse upper and lower gingival bleeding. Evidence of mucosal bleeding was observed in the nares bilaterally. Examination of the respiratory, cardiovascular and gastrointestinal systems were normal. The musculoskeletal exam was negative for active synovitis, subcutaneous nodules, joint swelling or erythema. On neurological exam, he responded appropriately, moving all limbs equally, with no focal neurological deficits noted.

His initial Complete Blood Count (CBC) could not be analyzed due to significant blood viscosity. The patient was started on Intravenous (IV) fluids and laboratory technicians used dilu-

tion techniques to be able to analyze his blood samples.

His labs eventually showed the following :White Blood Cell (WBC) 3.7 thousand/uL (RR:4.0-10.0 thousand/uL), hemoglobin 8.9 g/dl (RR:12.7-16.7 g/dL),platelets 101 thousand/uL (RR:140- 440 thousand/uL),serum total protein 9.7 g/dL(RR:6.0 to 8.0 g/dL),serum albumin 3.3g /dL (RR:3.5 to 5.5 g/dL), bilirubin total 0.8 mg/dL (RR:0.1 to 1.2 mg/dL),direct bilirubin < 0.2 mg/dL (RR:0.0 to 0.4 mg/dL),AST 84 IU/L (RR:10 to 55 IU/L),ALT 43 IU/L (RR:10 to 50 IU/L), alkaline phosphatase 112 IU/L (RR:45-115 IU/L), creatinine 0.8mg/dL (RR:0.5-1.2 mg/dL), and a BUN 19 mg/dL (RR:6-23 mg/dL). His urinalysis was abnormal with red blood cells (RBC) >182 RBC/HPF (RR:0-5 RBC/HPF).
Due to the concern for hyper viscosity syndrome, the patient was started on therapeutic plasmapheresis and a workup for hyper viscosity syndrome was pursued. He had significant improvement and subsequent resolution of his symptoms after three sessions of plasmapheresis.

His post-plasmapheresis labs showed the following: 372 mg/dL (RR:40-230 mg/dL), IgG 5040 mg/dL (RR:650-1600 mg/dL), IgA 690 mg/dL (RR:0-400 mg/dL), ANA titre: negative (RR: negative), dsDNA titre: > 1:5120 (RR: negative) with negative anti-RNP, anti-Sm, anti-SSB and anti-SSA antibodies. His complements, C3 and C4, were normal but his rheumatoid factor (RF) was 640 IU/mL (RR: negative) with anti-Cyclic Citrullinated Peptide IgG antibodies (anti-CCP) of 162.1 U (RR: negative). His C-reactive protein (CRP) was 0.1 mg/dL (0.0-0.7 mg/dL) and his ESR was 74 mm/hr (RR: 0-10 mm/hr). Eventually, the results for his serum viscosity became available (after his 2nd round of plasmapheresis)and was noted to be >5.6 cpoise (RR< 1.5 cpoise).
A bone marrow exam showed markedly hypercellular bone marrow with maturing trilineage proliferation and mild myelofibrosis. The associated flow cytometry did not show any evidence of a myeloproliferative disorder. An MRI brain with contrast did not reveal any intracerebral pathology. He had computer tomography (CT) exams of his chest, abdomen and pelvis, which did not find any evidence of malignancy. Given no evidence of a myeloproliferative process, there was more concern for an underlying autoimmune condition. He was treated with pulse dose IV methylprednisolone 1000 mg daily for three days followed by prednisone 70 mg daily, and he received one dose of 1000 mg Rituximab followed by another dose of 1000mg, two weeks later.
Upon follow up one month later, the patient was doing well with no bleeding, dizziness or blurry vision. He was on 50 mg of prednisone and was given instructions to taper his prednisone. Two months later his labs were repeated. His complete blood count was normal. Serum viscosity was 1.5 cpoise (RR<1.5 poise), IgG 2110 mg/dL (RR:650-1600 mg/dL), IgM 147 mg/dL (RR:40-230 mg/dL), IgA 344 mg/dL (RR:70-400 mg/dL) . Interestingly, his RF was still elevated at 640 IU/ml (RR: negative) and so was his anti-CCP 152.3 U (RR: negative) but his ANA titer was 1:640 diffuse pattern (RR: negative) and his DsDNA titer still > 1:5120 (RR: negative).
What was even more interesting was the development of significant symmetrical joint pain and swelling of the wrists, the Metacarpophalangeal (MCP) joints and the knees, when he was seen five months after his initial admission. These findings were noted after the complete taper of his prednisone. After his examination confirmed bilateral symmetrical synovitis, he was started on oral weekly methotrexate and low dose prednisone 10mg daily again, with a plan to administer a second course of rituximab- 1000mg, two weeks apart.

Discussion

Hyper viscosity syndrome (HVS), due to the presence of an underlying connective tissue disorder, has been described in the literature many times over. In fact, one of the earliest papers to describe the Rheumatoid Hyper viscosity Syndrome quite aptly summarized it as a conglomeration of nodular rheumatoid disease, bleeding diathesis, dyspnea and weakness, and palmar erythema, with high titer RF and serum hyperviscosity [1]. This definition has not changed much but a recent systematic review of 25 cases was able to define the frequency of these major clinical manifestations: bleeding diathesis (95%), heart failure (100%),altered mental status (100%), constitutional symptoms (100%) and blurred vision (92%).As expected, the majority of patients had impressively high titers of RF of 1:5120 (83%),polyclonal gamma globulins and positive ANA titers (82%).These were accompanied by anemia (90%) and leukopenia (47%) [2]. There are case reports of HVS being described in patients with long-standing deforming rheumatoid arthritis, in association with normocytic anemia and even cardiomyopathy [3].

Our patient, on the other hand, while he had features of hyper viscosity syndrome, he had no initial synovitis, rheumatoid nodules or other clinical stigmata of rheumatoid arthritis disease. Interestingly, he had a negative ANA and a very high dsDNA titer, which made his initial diagnosis somewhat difficult to define. This, in fact, is not a new phenomenon. High levels of rheumatoid factor, in association with intermediate complexes, have been known to mask the presence of other autoantibodies, such as the ANA and dsDNA [4].

HVS is felt to occur because of intermediate complex formation. These complexes are polymers of IgG, which have a high affinity for the IgM rheumatoid factor, forming even larger complexes, ultimately leading to the hyper viscosity features that define this syndrome [3]. Serum electrophoresis patterns of these patients reveal an elevated broad-based gamma globulin peak with associated hypoalbuminemia [1,3]. Treatment with prednisone and plasmapheresis decrease the IgG levels which are felt to be the predominant causative factor here. Other theories involve either the conglomeration of IgG intermediate complexes alone or the aggregation of immunoglobulins unto the Fc region of another immunoglobulin [4].

Doses of prednisone that range from 20-120mg /day have been used but this is usually accompanied by a relapse of 46% [2]. Similarly, monotherapy with plasmapheresis, which can range from 2-10 cycles, can result in recurrence rates of 43% [2]. This reoccurrence can occur anywhere from 1 month to 4 years after the initial presentation and treatment [2]. Plasma exchange can decrease plasma viscosity by 30-50% with one single session and typically,one session is needed to reduce viscosity to levels where mucosal hemorrhaging is halted.A maximum of three sessions is usually required when the serum viscosity exceeds 6 cpoise [5].
There have been cases reported where cyclophosphamide was added to plasmapheresis therapy with no relapses reported, and when this cytotoxic drug is added to prednisone, there is a decrease in the rick of reoccurrence. Chlorambucil has report-

edly been used in 4 patients, with a recurrence of 50%; as well as, hydroxychloroquine in combination with methotrexate. As with our patient, rituximab has been successfully utilized in one case report [6].

Given the lack of a uniform treatment protocol for this rare entity, and due to the severity of this patient's symptoms and the adverse effects of the syndrome on his life, the decision was made to use triple therapy- pulsed, high doses of steroids with plasmapheresis, followed by rituximab. This so-called triple therapy was working quite well for our patient until the clinical development of RA, which is in keeping with the B-cell reconstitution that follows rituximab administration.

It is important to recognize this entity, as heralded by specific manifestations due to mucosal hemorrhage (epistaxis, gingival and gastrointestinal bleeding) visual disturbances (bilateral retinal hemorrhages and thrombosis), neurologic (somnolence, seizure, ataxia, cerebral hemorrhage) and cardiac (high output heart failure) involvement, so that swift management can be instituted to prevent complications.

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