Hyperviscosity Syndrome in Rheumatoid Arthritis

To the Editor:

Hyperviscosity syndrome (HVS) is a life-threatening condition often occurring as a complication of Waldenström macroglobulinemia (WM) but rarely in the context of rheumatic disease. Given its rarity, diagnosis can be delayed, leading to greater morbidity. Our interest was sparked by a recent experience with a patient with rheumatoid arthritis (RA) who developed epistaxis with progressively worsening dyspnea, confusion, and visual deficits culminating in hospitalization due to HVS. As HVS is uncommon in the era of biologic medications, we conducted a systematic review (Supplementary Figure 1, available from the authors on request) to define factors that predispose to HVS and describe outcomes of previous treatment approaches. We identified 25 cases of hyperviscosity attributed to RA.

The most common presenting features for HVS included bleeding diathesis (e.g., epistaxis, gastrointestinal hemorrhage, gingival bleeding), heart failure (dyspnea and/or pedal edema), neurologic symptoms (dizziness, syncope, confusion), and constitutional symptoms (Table 1). RA developed years before HVS (7.9±7.4 yrs) but was the presenting manifestation in 3 cases. Synovitis was often active at time of diagnosis, and use of disease-modifying antirheumatic drugs prior to HVS was rare (n = 6). Retinopathy with venous distention was common and correlated with neurologic deficits. Adenopathy and/or splenomegaly occurred in over half the patients, and rheumatoid nodules were common. Features of rheumatoid vasculitis—scleritis/episcleritis, skin ulcers, and periungual infarcts—were described in 7 cases, with only half associated with cryoglobulins.

Rheumatoid factor (RF) was positive in all cases of HVS, with 83% (n = 18) having a titer > 1:5120. Mean serum viscosity was 10.7±12.5 cP. Polyclonal hypergammaglobulinemia was common, involving IgG, IgA, and IgM, though these were distinctly lower than levels associated with HVS in WM and multiple myeloma. Anemia was present in 90%, and neutropenia in 47%. One-third of the latter had known or suspected Felty syndrome; none had large granular lymphocytic leukemia or lymphoma. Only 1 patient had a monoclonal gammapathy. Antibodies to extractable nuclear antigens. Anti-dsDNA antibodies were positive in 2 cases with a homogenous staining pattern in titers > 1:640. Few cases reported antibodies to extractable nuclear antigens. Anti- dsDNA antibodies were positive in 2 patients. Sicca was documented in 4 cases, including 2 with abnormal Schirmer test.

Plasmapheresis was performed in 83% (19 of 23; Supplementary Table 1, available from the authors on request). The overall recurrence rate for HVS was 43% (10 of 23) at 11.3±14.7 months. After plasmapheresis, HVS recurred as early as 1 month and as late as 4 years. Plasmapheresis monotherapy was used in 4 cases, with all patients relapsing and requiring further intervention. Addition of prednisone, between 20–120 mg/day, was associated with a reduced risk of relapse at 46% (6 of 13). However, risk of relapse remained high on prednisone monotherapy, and 2 patients had recurrence once prednisone was discontinued. HVS recurred earlier without immunosuppression, often within 6 months. Of the 23 cases reporting treatment and outcome, 4 patients were managed without plasmapheresis, 2 of whom had early recurrence of symptoms. Prednisone, 40–60mg daily, and cyclophosphamide (CYC), without the use of plasmapheresis, decreased the risk of recurrence in the acute setting.

Immunosuppression reduced the risk of HVS recurrence after plasmapheresis. There were no recurrences in patients treated with CYC (0 of 3), one of whom was treated during the initial presentation and 2 during HVS recurrence. Addition of chlorambucil reduced recurrence to 50%.
RA and is related to Ig and fibrinogen levels, though this may not be fully appreciated with serum viscosity.

HVS is a rare complication of RA, especially in this era of effective disease-modifying therapy. This should be considered in patients with longstanding, seropositive RA presenting with bleeding diathesis, dyspnea and/or altered mentation, especially those with active synovitis, high RF, marked erythrocyte sedimentation rate elevation, anemia, and/or hypergamma-globulinemia. Early identification and treatment are important to prevent complications, and diagnosis is confirmed by checking viscosity level. In patients with HVS, plasmapheresis followed by further immunosuppression is recommended. CYC has the most data available; however, there is a paucity of data for HVS maintenance therapy in RA. The relationship to RF titer and intermediate complexes supports the use of RTX, and this has been effective in our patient.

John B. Miller, MD
Alan N. Baer, MD
Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
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Address correspondence to Dr. J.B. Miller, Instructor of Medicine, 5200 Eastern Ave., Mason F. Lord Building Center Tower, Suite 4100, Baltimore, MD 21224, USA. Email: JMill237@jhu.edu.

REFERENCES