

Letter

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 HVS¹. 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 gammopathy. Antinuclear antibody was often positive with a homogenous staining pattern in titers $> 1:640$. Few cases reported antibodies to extractable nuclear antigens. Anti-dsDNA antibodies were reported 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%

Table 1. Features of hyperviscosity in the setting of rheumatoid arthritis.

	Values
Age, yrs, mean \pm SD	52 \pm 14.7
Disease duration, yrs, mean \pm SD	7.9 \pm 7.4
Sex, female, %	76
Symptoms, %	
Bleeding diathesis	95 [n = 22]
Heart failure	100 [n = 18]
Altered mental status	100 [n = 16]
Constitutional symptoms	100 [n = 14]
Blurred vision	92 [n = 13]
Previous therapy, n	
NSAID/salicylates	9
Corticosteroids	5
DMARD ^a	6
Examination findings, %	
Active synovitis	86 [n = 22]
Retinopathy	86 [n = 21]
Adenopathy or splenomegaly	69 [n = 16]
Rheumatoid nodules	100 [n = 8]
Laboratory tests	
ESR > 100 mm/h, %	68 [n = 19]
Positive RF (\bar{x}_g/\bar{x}), IU, mL	1:12,233 [n = 18] / 19,869 IU/mL [n = 3]
Positive ACPA, %	100 [n = 2]
Total protein, g/dL	9.8 \pm 1.4 [n = 14]
Albumin, g/dL	2.9 \pm 0.9 [n = 8]
Serum viscosity ^b , cP	10.7 \pm 12.5 [n = 23]
Mean IgG, mg/dL	3559 \pm 2225 [n = 19]
Mean IgA, mg/dL	1075 \pm 817 [n = 19]
Mean IgM, mg/dL	1263 \pm 1225 [n = 19]
WBC < 4000 , %	48 [n = 21]
Mean hemoglobin, g/dL	9.9 \pm 2.3 [n = 20]
Positive ANA, %	82 [n = 22]
Low complement ^c , %	38 [n = 13]
Cryoglobulinemia, %	32 [n = 19]

Percentage of symptoms and examination findings are calculated based on case reports describing that particular feature, represented in brackets [].

^a DMARD include methotrexate ($n = 2$), gold ($n = 2$), penicillamine ($n = 2$), leflunomide ($n = 1$), and azathioprine ($n = 1$). ^b Two cases reported either whole blood or plasma viscosity. ^c Four cases with C3 and C4 hypocomplementemia and 1 with isolated C3 hypocomplementemia; only 1 of these patients had cryoglobulinemia. ACPA: anticitrullinated protein antibody; ANA: antinuclear antibody; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; NSAID: nonsteroidal antiinflammatory drug; RF: rheumatoid factor; WBC: white blood cell.

(2 of 4). Addition of methotrexate with hydroxychloroquine was effective at preventing recurrence for 1 patient with HVS. Rituximab (RTX) was successful in 1 patient and is often used for HVS related to WM².

HVS in RA can occur with levels of Ig much lower than in WM³. In RA, this has been attributed in part to aggregations of Ig, termed *intermediate complexes*, which have a sedimentation coefficient between that of monomeric IgG and pentameric IgM⁴. Different intermediate complexes have been associated with hyperviscosity, including either IgG or IgM RF aggregating with polyclonal Ig^{5,6}. In Sjögren syndrome, the degree of hyperviscosity correlates directly with the titer of the RF in addition to disease activity⁷. Erythrocyte aggregation is also an important feature of HVS in

RA and is related to Ig and fibrinogen levels, though this may not be fully appreciated with serum viscosity⁸.

HVS is a rare complication of RA, especially in this era of effective disease-modifying therapy. This should be considered in patients with long-standing, 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 hypergammaglobulinemia. 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.

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