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CASE REPORT

A Case of Hyperviscosity Syndrome in Rheumatoid Arthritis

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Abstract
Hyperviscosity syndrome (HVS) is a rare complication of both monoclonal and polyclonal disorders associated with elevation of immunoglobulins. Here, we describe a female patient who presented with shortness of breath and a history of seropositive rheumatoid arthritis with deformities, significant barriers to care, and poor therapeutic adherence. Her rheumatoid factor titer was greater than 1000 kIU/L, and she had an elevated serum viscosity level with her presentation consistent with HVS which improved significantly after therapeutic plasmapheresis. Our case highlights the presentation of rare but potentially life-threatening HVS that can occur in patients with systemic autoimmune rheumatic disorder.

Background
Hyperviscosity syndrome (HVS) may be a life-threatening condition that can be seen in patients with systemic autoimmune rheumatic disease. Diagnosis is based on clinical symptoms tied to elevated serum viscosity (1–3). We describe a patient with seropositive rheumatoid arthritis (RA) who presented with shortness of breath who was diagnosed and successfully treated for HVS.

Objective
Highlight the presentation of HVS in patient and its relationship to systemic autoimmune rheumatic disease, including RA.

Case Report
A 61-year-old woman presented to the emergency department with worsening dyspnea. Over the previous 6 months, she noted gradual worsening with acute exacerbation of dyspnea. She had dyspnea on exertion, 2-pillow orthopnea, and fatigue, with a dry cough and swelling of bilateral lower limbs worse in the evenings. A week before presentation, she had 1 episode of lightheadedness. She had no chest or abdominal pain, fever, chills, nonintentional weight loss, polydipsia, polyuria, joint swelling, rashes, oral or nasal lesions, palpitations, nausea, vomiting, or diarrhea.

She was diagnosed with seropositive RA 20 years before this presentation with unknown Clinical Disease Activity Index (CDAI)/Simplified Disease Activity Index score at initial assessment. RA was complicated with usual interstitial pneumonia pattern interstitial lung disease 4 years before this presentation and keratoconjunctivitis sicca. She did not have pulmonary artery hypertension or congestive heart failure.

She had been prescribed etanercept, 50 mg, methotrexate 15 mg, hydroxychloroquine, 400 mg, and carvedilol, 12.5 mg twice daily. Due to significant barriers to care, therapeutic adherence was poor. Despite being prescribed triple therapy, she was unable to access these medicines. She was not on any complementary and alternative therapies. Her previous surgeries included tonsillectomy and partial hysterectomy. She was a nonsmoker and did not consume alcohol or use complementary and alternative medicine. Her blood pressure 18.398/11.466 kPa, pulse rate of 85 beats/min, and temperature 96.5 °F (35.8 °C), with a body mass index of 16.3 kg/m^2. Her

respiratory rate was 20 breaths/min, and oxygen saturation was 93% on 3 liters of oxygen. She was alert but chronically ill-looking and cachexic. She did not have increased work of breathing, not using accessory muscles of respiration, and breath sounds were normal to auscultation. There was no jugular venous distention, and her heart sounds were normal.

Her pupils bilaterally equal and reactive to light. No conjunctival injection or scleral icterus was noted. She had no skin rashes, ulcerations, palpable purpura, or nodules. She had no palpable lymph nodes. Her abdomen was soft, nontender, and nondistended with normal bowel sounds. Her muscle tone was normal, power was 5/5, and no cranial nerves did deficits were noted. She had bilateral ulnar deviation at the metacarpal phalangeal joints with swan neck deformities at third and fourth fingers bilaterally. There was no joint swelling, warmth, or redness, but tenderness was noted.

Laboratory tests with reference ranges are shown in Table 1. Her rheumatoid factor was greater than 1000 kIU/L on day 1 of admission, with IgM level of 5.980 g/L and a protein gap of 95 g/L. The serum electrophoresis confirmed an elevated kappa-to-lambda ratio without M-spike. Her serum sodium of 123 mmol/L, consistent with pseudohyponatremia in this setting, and serum viscosity level was 13.7 relative to H_2O.

Computed tomography angiography scan of the chest showed pulmonary edema but not pulmonary embolism. Her echocardiogram confirmed left ventricular ejection fraction to 45% to 50%.

Rheumatology, nephrology, pulmonology, and hematology services were consulted. A diagnosis of active RA-related HVS was made based on her clinical symptoms and elevated serum viscosity. Serum protein electrophoresis did not show a monoclonal protein spike (Table 1), and ultrasound-guided abdominal fat pad biopsy was negative for amyloid. Age- and sex-appropriate malignancy screening was unremarkable and, based on all of the information, a final diagnosis of RA-related HVS was made.

She was treated with 3 cycles of plasma exchange, with improvement in her HVS-related symptoms, laboratory, and echocardiogram indices. As her CDAI was 30 on admission, her RA therapies were altered, she was enrolled in our hospital systems medication assistance program and started on hydroxychloroquine, 200 mg once daily, and rituximab. She has completed the rituximab starting dose infusions, 1000 mg each 14 days apart, and she is maintained on 500-mg infusions every 6 months. Her most recent serum viscosity is 2.3 relative to H_2O, and she has sustained symptomatic improvement. Her most recent CDAI is 5, indicating clinical remission of her RA.

Table 1. **Laboratory Test***

Blood Test/Reference Range	Day 1	Day 9
Serum sodium (135–145 mmol/L)	**123**	136
Serum albumin (32–55 g/L)	**41**	40
Serum globulin (17–39 g/L)	**21**	
Total protein (61–81 g/L)	**116**	69
Serum creatinine (44.21–79.58 μmol/L)	<33.6	
Urea nitrogen (2.14–7.14 mmol/L)	5.36	
Aspartate aminotransferase (10–42 IU/L)	52	
Alanine aminotransferase (10–60 IU/L)	38	
Alkaline phosphatase (42–121 IU/L)	40	
Total bilirubin (<20.52 μmol/L)	6.84	
Rheumatoid factor (>14 kIU/L)	**>1000**	**464**
Complement C3 (0.9–1.8 g/L)	0.79	
Complement C4 (0.1–0.4 mg/L)	0.114	
Serum viscosity (1.5–1.9 relative to H_2O)	**13.7**	**2.2**
Myeloperoxidase autoantibody (<1.0 AI)	<1.0 AI	
Proteinase-3 autoantibody (<1.0 AI)	<1.0 AI	
ANCA screen (Negative)	Negative	
Cryoglobulin (none detected)	None detected	
ANA† (<1:40)	**Positive, >1:1280**	
Anti DsDNA (>10 000 IU/L)	5000	
Thyroid peroxidase (TPO) antibody (34 kIU/L)	<9	
Ribosomal P protein antibody (0.0–1.0 AI)	<1.0	
Scleroderma (SCL-70) antibody (0.0–1.0 AI)	<1.0	
Sjogren's antibody SSA (0.0–1.0 AI)	<1.0	
Sjogren's antibody SSB (0.0–1.0 AI)	<1.0	
Anti-Smith antibody (0.0–1.0 AI)	<1.0	
U1RNP antibody (0.0–1.0 AI)	<1.0	
IgG (6.94–16.18 g/L)	12.49	
IgM (0.048–0.171 g/L)	**5.980**	
IgA (0.810–4.630 g/L)	2.890	
Total protein (61–81 g/L)	116	
Albumin (38–55 g/L)	21	
Alpha 1 globulin (2–3 g/L)	4	
Alpha 2 globulin (5–9 g/L)	8	
Beta 1 globulin (4–6 g/L)	6	
Beta 2 globulin (2–5 g/L)	12	
Gamma globulin (8–17 g/L)	67	
Kappa, quantitative (1.760–4430 g/L)	14.5	
Lambda, quantitative (0.91–2.4 g/L)	6.28	
Kappa/lambda ratio (1.29–2.55)	2.31	
M-spike (No M-spike detected)	No M-spike detected	

ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; ENA = extractable nuclear antigen; Ig = immunoglobulin; M-spike = monoclonal spike; NEG = negative; U1RNP = U1 small nuclear ribonucleoprotein.
*Boldface values indicate abnormal laboratory values pertinent to the case.
†ANA detection method by indirect immunofluorescence technique; Ig detection by enzyme-linked immunosorbent assay.

Discussion

Serum proteins like immunoglobulin play a significant role in serum viscosity. IgM is the largest immunoglobulin, with a molecular weight of 950 kDa (3). Larger linear proteins like IgM have a disproportionate impact on viscosity (4, 5). In total, 80% of total body IgM is intravascular and 20% is tissue bound (3–5). The high axial length-to-width ratio of IgM causes it to spin end-over-end, further raising serum viscosity disproportionately when compared with other serum proteins (3). A relatively small change in IgM concentration can therefore have a significant impact on serum viscosity.

In the era of effective disease-modifying therapy for RA, HVS is rare. Our patient had not been on therapy for her RA. Her high levels of autoantibodies increase the risk for HVS (1, 2, 6). Rheumatoid factors (RFs) are autoantibodies of various immunoglobulin subtypes, directed against the Fc portion of IgG (7). The most commonly RF subtype is IgM RF (7). Our patient had high IgM levels, resulting in elevated serum viscosity. Hypergammaglobulinemia and elevated serum viscosity occur in RA but in HVS are rare, although they may occur in the absence of joint disease (1, 4). Hyponatremia may be seen and relates to the net positive charge on immunoglobulins (6, 8).

Common modes of presentation of HVS include bleeding diathesis, heart failure, and neurologic symptoms. Other symptoms include visual changes and anorexia. The nonspecific symptoms lead to significant diagnostic delays and in increased morbidity and mortality (1–4). A high index of suspicion allows for early identification and treatment to prevent complications (4, 9).

Therapeutic plasma exchange (TPE) is an effective treatment, as it removes the serum proteins causing the HVS (9, 10). TPE has been successfully used since the late 1950s and has been shown to promptly reverse both serum viscosity and clinical manifestations of HVS (9, 10). Each cycle of TPE can reduce viscosity by up to 20% to 30% (9). The therapeutic goal of TPE is to lower the serum viscosity below the symptomatic threshold of the individual patient. TPE does not affect the underlying disease process, and in rheumatic disease–induced HVS, systemic immunosuppressive therapy should also be initiated after TPE is completed (9, 10).

References

1. Miller JB, Baer AN. Hyperviscosity syndrome in rheumatoid arthritis. J Rheumatol. 2021;48:788-9. [PMID: 33452169] doi:10.3899/jrheum.200591
2. Perez Rogers A, Estes M. Hyperviscosity Syndrome. 2023 Mar 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. [PMID: 30085505].
3. Gertz MA. Acute hyperviscosity: syndromes and management. Blood. 2018;132:1379-85. [PMID: 30104220] doi:10.1182/blood-2018-06-846816
4. Zakzook SI, Yunus MB, Mulconrey DS. Hyperviscosity syndrome in rheumatoid arthritis with Felty's syndrome: case report and review of the literature. Clin Rheumatol. 2002;21:82-5. [PMID: 11954894] doi:10.1007/s100670200020
5. Bach LA, Buchanan RR, Scarlett JD, et al. Hyperviscosity syndrome secondary to rheumatoid arthritis. Aust N Z J Med. 1989;19:710-2. [PMID: 2631664] doi:10.1111/j.1445-5994.1989.tb00341.x
6. Mirvis E, De-Silva D, Mehta A. Hyponatraemia in patients with multiple myeloma. BMJ Case Rep. 2015; bcr2015212838. [PMID: 26655670] doi:10.1136/bcr-2015-212838
7. Ingegnoli F, Castelli R, Gualtierotti R. Rheumatoid factors: clinical applications. Dis Markers. 2013;35:727-34. [PMID: 24324289] doi:10.1155/2013/726598
8. Koumpis E, Florentin M, Hatzimichael E, et al. Hyponatremia in patients with hematologic diseases. J Clin Med. 2020;9:3721. [PMID: 33228240] doi:10.3390/jcm9113721
9. Lokhandwala PM, Shabihkhani M, Ness PM, et al. Therapeutic plasma exchange for hyperviscosity syndrome secondary to high rheumatoid factor. Transfus Apher Sci. 2018;57:225-7. [PMID: 29478798] doi:10.1016/j.transci.2018.02.004
10. Padmanabhan A, Connelly-Smith L, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the Writing Committee of the American Society for Apheresis: the Eighth Special Issue. J Clin Apher. 2019;34:171-354. [PMID: 31180581] doi:10.1002/jca.21705