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Clinical Reports

Hyperviscosity Syndrome Complicating Rheumatoid Arthritis: Report of Two Additional Cases and Review of the Literature

Michael R. Lovy, MD,* Mark C. Kranc, MD, Gilbert B. Bluhm, MD,*** Jeanne M. Riddle, PhD,*** and Paul D. Stein, MD******

A hyperviscosity syndrome developed in two patients with rheumatoid arthritis. Analytic ultracentrifugation of the sera from one patient demonstrated 22S complexes. Intermediate, 22S, and 31S complexes were found in the second case. Platelet aggregometry and electron microscopy surveys of the platelet reactivity in one patient demonstrated inhibition of platelet reactivity caused by the presence of the high molecular weight complexes. These abnormalities, as well as the clinical bleeding, whole blood, and plasma viscosity, became normal after treatment. In vivo leukocytic function was studied with the Rebuck skin window technique, and phagosomal inclusions were observed in both the polymorphonuclear neutrophils and macrophages.

Hyperviscosity syndrome is characterized by abnormalities affecting multiple organ systems. Retinal hemorrhages, congestive heart failure, neurologic and hemostatic abnormalities, and symptoms of anorexia, fatigue, and malaise are its manifestations. Although hypergammaglobulinemia and elevated serum viscosity frequently occur in patients with rheumatoid arthritis (1), they rarely reach levels necessary to produce hyperviscosity syndrome.

Among the reported cases of hyperviscosity syndrome complicating rheumatoid arthritis (2-8), the specific immunoglobulin abnormality causing the increased viscosity has varied. These abnormalities include polymers of IgG, which showed rheumatoid factor activity and cryoglobulin properties (2), IgG rheumatoid factor circulating as a polyclonal 13S component (4), intermediate complexes formed by self-association of IgG rheumatoid factor molecules (6), and interaction of IgM rheumatoid factor with intermediate complexes (3,7).

We have observed two additional patients with a hyperviscosity syndrome complicating rheumatoid arthritis. By the use of analytic ultracentrifugation, we were able to demonstrate 22S complexes in the sera of one patient and high molecular weight complexes in the other. These complexes were responsible for the hyperviscosity. The bleeding diathesis was studied in each patient. In the second patient, platelet aggregation and electron microscopic studies of the platelet reactivity suggested that intermediate and high molecular weight proteins were capable of altering platelet morphology and interfering with in vitro platelet aggregation.

Case Reports

Case 1

A 43-year-old black woman was admitted to Henry Ford Hospital in April 1969 because of anorexia, weight loss, fatigue, and frequent nosebleeds. She had been well until 1966, when she developed rheumatoid arthritis. She had numerous extra-articular manifestations of rheumatoid arthritis, including subcutaneous nodules, leg ulcers, a rheumatoid pleural effusion, and Sjogren's syndrome.

On examination, there were decreased breath sounds at the base of the right lung, but no signs of active synovitis. Laboratory results included the following: hemoglobin 11.3 gm%, white blood cell count 4,000/mm^3, with 44% polymorphonuclear cells, 3% eosinophils, 1% basophils, 15% lymphocytes,

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*Present Address: 1901 Cedar, Suite 201, Tacoma, Washington 98405
**2570 Haymaker Rd, Monroeville, Pennsylvania 15146
***Department of Internal Medicine, Rheumatology Division, Henry Ford Hospital
****Department of Internal Medicine, Division of Cardiovascular Medicine, Henry Ford Hospital
Address reprints to Dr. Bluhm, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202

32% atypical lymphocytes, and 5% monocytes. The erythrocytes showed marked rouleaux formation and numerous target cells. The platelet count was 442,000/mm³. The relative serum viscosity was 6.0 (normal 1.2-2) (9). Other laboratory parameters included: erythrocyte sedimentation rate (ESR) 1mm/hr (Wintrobe method), lupus erythematosus (L.E.) cell preparation positive, strong homogeneous antinuclear factor, sodium 131 mEq/1, chloride 103 mEq/1, and Co_2 combining power 23 mEq/1, total protein 8.8 g/dl, gamma globulin 5.0 g/dl, IgG 4,640 mg/dl, IgM 2,347 mg/dl, and IgA 280 mg/dl. Examination of the bone marrow aspiration showed lymphocytosis, plasmacytosis, and slight eosinophilia. The following tests were either negative or normal: rheumatoid factor agglutination titer (10), urinalysis, metastatic survey, 24-hour urine for protein and immunoglobulin electrophoresis, serum cryoglobulins, sickle cell preparation, VDRL, total hemolytic complement, acute and convalescent viral antibody titers for polio types 13, Echo 6, 9, and Coxsackie A-9, B1, B5, alkaline phosphatase, SGOT, and BSP retention. A survey of the plasma coagulation system showed that the Lee-White and plasma clotting time, fibrin stabilization factor, tests for circulating anticoagulants, and factor IX assay were normal. Before the patient received any therapy, coagulation studies showed abnormal results, with a bleeding time of eight minutes, activated partial thromboplastin time (APTT) of 98 seconds (control: 64 seconds), poor clot retraction, and a two-stage PTT assay for factor VIII of 74%.

During her hospitalization, she developed bleeding of the gums, and cyclophosphamide (150 mg/day) was given orally. One week later, when she developed a pericardial friction rub and congestive heart failure, therapy with prednisone (60 mg/day) was added to the treatment regimen. Within one week she showed improvement of the congestive heart failure, her appetite returned, and bleeding ceased. Coagulation studies were normal three weeks after the cyclsphosphamide medication had been initiated.

By June 1969, the patient was doing well on prednisone 10 mg/day and cyclosphosphamide 50 mg every other day. The relative serum viscosity (11-13) was 1.75, total protein 6.8 gm/dl, gamma globulin 1.6 g/dl, IgG 1,244 mg/dl, IgM 384 mg/dl, IgA 153 mg/dl (14), and rheumatoid factor titer 1:320 (15). Subsequent doses of medications and corresponding laboratory results were correlated (Fig. 1).

Rheumatoid erosions of the interphalangeal joints, as demonstrated radiographically, and rheumatoid factor activity in the synovial fluid were subsequently shown. Over the following eight years, she had infrequent flares of arthritis. Treatment with indomethacin, aspirin, and prednisone (5 mg/day) was continued. She was last seen in the Rheumatology Clinic at Henry Ford Hospital in December 1978.

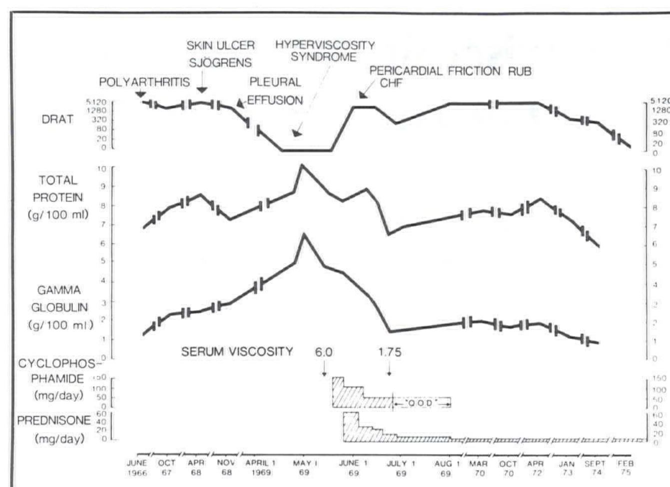

Fig. 1

Clinical and laboratory course of Case 1. DRAT = differential rheumatoid agglutination titer. Normal range for relative serum viscosity is 1.2-2.

Case 2

A 60-year-old black man, with a six-year history of arthritis, was admitted to Henry Ford Hospital in September 1978 with headaches, episodic dizziness with an unsteady gait, dyspnea on exertion, orthopnea, weakness, malaise, bleeding from his gums of two months' duration, and a weight loss of 15 pounds. In the month before he was admitted, he had noted increased morning stiffness and pain with swelling in his joints.

He was in no acute distress, afebrile, his blood pressure was 140/90 mm Hg, and he had a regular pulse of 100/min. His cheeks were erythematous. The retinal veins were distended, and there were scattered hemorrhages and exudates. He had only limited movement of his jaw. He had bilateral contractures with crepitation and synovial thickening of the elbows and wrists, ulnar deviation of the hands with symmetrical deformity of the metacarpal phalangeal and proximal interphalangeal joints, and a moderate effusion in the right knee. No subcutaneous nodules were present.

The hemoglobin was 9.5 gm%, the white blood cell count 5,800/mm³, with a normal differential count except for an occasional atypical lymphocyte and mononuclear cells resembling Mott cells (Fig. 2A). The platelet count was 201,000/mm³. The erythrocytes showed moderate rouleaux formation. Rheumatoid factor titer was 1:20,480 (15). Laboratory results are summarized in Tables I and II. Serum protein electrophoresis demonstrated a gamma globulin peak of 5.9 g/dl with restricted mobility. A 24-hour urine collection contained a trace amount of free kappa chains, but no Bence-Jones protein. Bone marrow aspiration showed an atypical lymphocytosis and an increased number of plasma cells, some of which showed Russell bodies (Fig. 2B). Westergren sedimentation rate was 58 mm/hr, antinuclear factor was positive; sodium 130 mEq/1, chloride 105 mEq/1, and CO_2 combining power was 21 mEq/1. The following tests were either normal or negative: urinalysis, L.E. cell preparation, serum cryoglobulins, hepatitis B antigen and antibody, heterophile antibody, serum uric acid, blood urea nitrogen, creatinine, bilirubin, SGOT, LDH, alkaline

phosphatase, calcium, phosphorus, and Schirmer's test. A PPD skin test was 15 mm. Peripheral T and B cell studies were normal, including E, EA, and EAC rosettes, surface immunoglobulins, and mitogen stimulation with phytohemagglutinin, concanavalin A, and pokeweed mitogen (16,17).

Coagulation studies showed that the bleeding time, Lee-White clotting time, PT, APTT, fibrinogen, prothrombin consumption, factor VIII activity, and platelets were normal. Clot retraction was 1+ at one hour and 2+ at two hours. There was in vitro resistance to platelet aggregation by standard tests with epinephrine, adenosine diphosphate, and ristocetin (Fig. 3A). Initially, platelet reactivity as seen by transmission electron microscopy showed a decreased ability of individual platelets to extrude cytoplasmic pseudopodia (Fig. 4A).

Chest radiographs showed a slight prominence of the pulmonary vasculature and calcified hilar nodes. Extensive erosive changes of the interphalangeal joints were evident radiographically. M-mode echocardiography and systolic time intervals demonstrated normal left ventricular function.

Plasmapheresis of 1000 cc of blood was performed on five consecutive days. The patient noted improvement in his dizziness, headaches, mucous membrane bleeding, and joint symptoms within five days after the plasmapheresis was completed. During this time, the serum viscosity and gamma globulin concentration decreased by more than 50% (Table I). The patient was discharged on prednisone (120 mg every other day) and 300 mg of isonicotine hydrazine (INH) daily.

On October 12, 1978, repeat platelet aggregation studies revealed normal aggregability (Fig. 3B). Platelet reactivity, evaluated by electron microscopy, showed a hyperactive response. The platelet differential count was dominated by the spread type platelet, which accounted for 72% of the platelets (Fig. 4B). Clot retraction was 3+ at one hour and 4+ at two hours; the other coagulation tests were unchanged from previous studies. Peripheral T and B cell studies were again normal. Additional follow-up studies are shown in Tables I and II.

Over the next three months the patient remained asymptomatic, apart from continued active synovitis. The dosage of prednisone was changed to once a day and gradually reduced to 15 mg/day over the next three months. On April 10, 1979, the patient suffered multiple gunshot wounds and died.

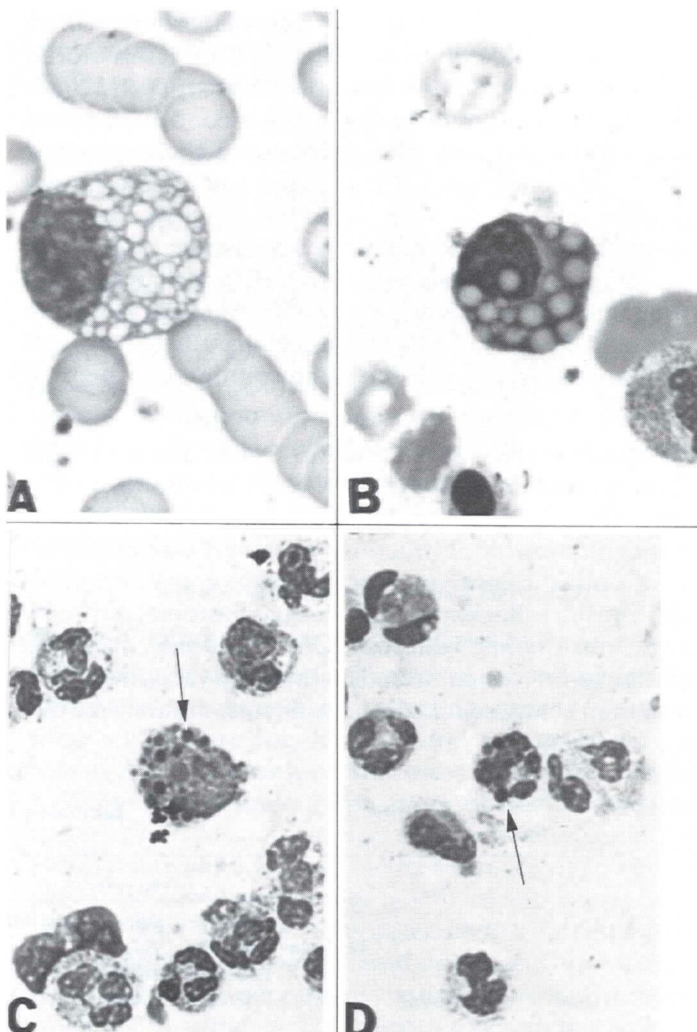

Fig. 2
Case 2

A. Mott cell and rouleaux formation in peripheral blood (X 1430); B. Plasma cell with Russell bodies from bone marrow (X 1430); C. Macrophage; and D. Polymorphonuclear cell containing large cytoplasmic inclusions (arrows) from a Rebuck skin window lesion at 12 hours (X 715). Leishman stain was used in all preparations.

Materials and Methods

The relative viscosity was determined with one milliliter samples of sera using a red blood cell pipette viscometer at 37°C (9). Whole blood and plasma viscosities were measured with a Wells-Brookfield cone-plated viscometer (Brookfield Engineering Laboratories, Inc, Stoughton, MA) at 37°C and a shear rate of 180 sec^{-1}.

Serum protein electrophoresis was performed using a Spinco cell with barbital buffer (pH 8.6) at 22°C. Serum immunoglobulin levels were quantitated by the microdouble diffusion technique (14). We performed immunoelectrophoretic studies with agarose gel using antiserum monospecific for IgG, IgM, IgA, and lambda and kappa chains (Meloy, Springfield, VA).

In the first patient, rheumatoid factor activity was determined by the sensitized sheep red blood cell agglutination test after the test serum was absorbed overnight with sheep red blood cells (10). In the second patient, rheumatoid factor activity was measured by latex agglutination (15) (Difco, Detroit, MI).

Analytical ultracentrifugation was performed with a Beckman Model E ultracentrifuge. In Case 1, sera stored at 4°C was used and centrifuged at 60,000 rpm and 20°C. Sera from Case 2 obtained after the second day of plasmapheresis and one month later and then stored at -20°C was centrifuged at 57,692 rpm and 22°C in 12 mm double sector cells with sapphire windows. Samples were diluted 1:5 with 0.01 M potassium phosphate buffer (pH 7.3) containing 0.15 M NaCl and dialyzed with the same solution overnight at 4°C. Aliquots were also diluted 1:5 with 0.05 M sodium acetate, 0.15 M NaCl (pH 4.0), and dialyzed with the same solution overnight at 4°C.

Agar gel filtration using both Bio-Gel A1.5 and A15 (Bio Rad, Richmond, CA) in 0.15 N NaCl was performed at neutral pH on plasma from Case 2 stored at 4°C. Protein concentration of all fractions obtained was estimated with optical density measurements at a wavelength of 280 nm in a Beckman DU Spectrophotometer (Beckman Instruments, Fullerton, CA). Fractions containing protein were concentrated 30 times by vacuum dialysis and then analyzed for cryoprecipitates, rheumatoid factor activity, immunoelectrophoretic pattern, and immunoglobulin level using methods described above. The Bio-Gel columns were calibrated with molecular weight markers, including dextran blue and purified human IgM, IgG, and albumin. Serum deletion of IgM was prepared by dialysis of serum at 4°C against deionized water at neutral pH. Afterwards, viscosity and immunoelectrophoretic patterns were determined.

Platelet aggregation studies of Case 2 used citrated whole blood and were performed with a BIO/DATA Platelet Aggregation Profiler[R] using ristocetin (1.2 and 2.0 mg/ml) adenosine diphosphate (0.8 mg/ml), adrenalin hydrochloride (1.0 mg/ml), and collagen. The platelet reactivity was determined by means of transmission electron microscopy (19).

Skin windows were prepared as described by Rebuck and Crowley (20) by abrading a single site on the forearm and applying tetanus toxoid. Coverslips which served to collect the inflammatory exudate were changed at 6, 12, 24, and 36 hours. The adherent cells were stained with Leishman stain, and a differential count on 500 cells was performed on each coverslip.

TABLE I

Laboratory Results of Case 2

Date	Treatment	Hematocrit (%)	Viscosity: Relative Serum (normal: 1.2-2)	Viscosity: Whole Blood* (180 sec⁻¹) (poise)	Viscosity: Plasma	Total Protein (g/dl)	Gamma-globulin (g/dl)	Immunoglobulins** IgG (mg/dl)	IgM (mg/dl)	IgA (mg/dl)	Rheumatoid Factor Titer
Case 2											
9/9/78	none	29	8.0			10.1	5.9	3810	2230	310	20,480
9/11	plasmapheresis										
9/12	plasmapheresis	32		.099	.059	8.0	2.25	2009	2260	237	
9/13	plasmapheresis	31		.088	.049	7.5	2.16	2359	2863	221	
9/14	plasmapheresis	33		.072	.039						
9/15	plasmapheresis	33		.063	.035						
9/19	prednisone (120 mg q.o.d.)	33	3.7	.064	.036	9.9	3.22				
10/12	prednisone (80 mg q.o.d.)	39		.044	.018	7.6	2.66	1748	688	347	40,960
12/6	prednisone (40 mg q.o.d.)			.045	.013	7.2	1.86	1075	319	116	5,120
1/12/79	prednisone (30 mg q.o.d.)					6.7	1.63				
3/22/79	prednisone (20 mg/day)					7.2	1.07				1,280

*The viscosity of whole blood of normal subjects in our laboratory ranged between .037 and .048 poise, and plasma ranged between .013 and .017 poise (11). These values of whole blood viscosity are comparable to those reported by Rosenblatt, et al (12) using a shear rate of 230 sec^{-1}; the values of plasma viscosity are comparable to those reported by Larcan, et al (13) using a shear rate of 230 sec^{-1}.

**Normal values in our laboratory range from 600 to 1400 for IgG, 50 to 250 for IgM, and from 50 to 150 for IgA (14).

Results of Special Studies

Analytical ultracentrifugation

Schlieren patterns of serum obtained from Case 1 (Fig. 5A) showed a 22S peak, which comprised approximately 27% of the total protein, but no evidence of intermediate complexes was obtained.

Schlieren patterns of serum obtained from Case 2 after two days of plasmapheresis showed fractions sedimenting at 4.19S, 7.79S, 13.37S, 22.13S, and 31.36S (Fig. 5B). Dialysis of the same serum in acid buffer resulted in the loss of intermediate and high molecular weight complexes and an increase in 16.55S and 6.28S peaks (Fig. 5C). Serum obtained after one month of prednisone therapy also contained intermediate 9.6S and 22S complexes, but they were present in smaller quantity (Fig. 5D).

Serum immunoelectrophoresis (Case 2)

Immunoelectrophoresis of pretreatment serum from Case 2 demonstrated precipitate around the origin and a double arc pattern of the precipitin line with all antisera used except anti-IgA (Fig. 6). This pattern indicates an IgG-IgM interaction. Serum depleted of IgM also failed to demonstrate a double arc pattern or precipitate around the origin.

Gel filtration (Case 2)

Separation of the immunoglobulins with a calibrated Bio-Gel A15 column (Fig. 7) revealed proteins ranging in size from 1.6×10^5 to 2.6×10^6 molecular weight. Fractions containing proteins had molecular weights of 2.6×10^6, 2.2×10^6, 9.0×10^5, 4.5×10^5, 2.8×10^5, and 1.6×10^5. Fractions with the heaviest molecular weights contained more IgG than IgM. Rheumatoid factor activity, cryoprecipitate, and abnormal double arc precipitin lines on immunoelectrophoresis were found exclusively in the IgM containing fractions. Small amounts of protein with molecular weight other than 9.0×10^5 (IgM) and 1.6×10^5 (IgG) were present in the post-treatment serum.

Viscosity determinations (Case 2)

Plasma from Case 2 obtained after two days of plasmapheresis was separated into a fraction depleted of IgM and one with IgM alone. The viscosities of the whole plasma and these fractions were 0.059, 0.010, and 0.0125 poise, respectively. Neither fraction alone, therefore, could account for the hyperviscosity of the original plasma specimen. Dithiothreitol was added to the plasma sample in an amount needed to abolish all rheumatoid factor activity measured by latex agglutination. After 30 minutes of incubation with dithiothreitol at room temperature, the viscosity of the plasma decreased from 0.047 to 0.023 poise.

Assessment of Platelet Function

Electron microscopic evaluation (Case 2)

The ability of the platelets from the second patient to adhere to a standardized activating surface (Formvar film) and cohere together to form an aggregate was assessed in vitro before and after treatment. Before treatment, the platelet population showed a decreased capacity to extrude pseudopodia, as evidenced in the platelet differential count by the presence of an abnormally increased percentage (34%) of the round type platelet. Pair-wise contrasts based on the percentage of the round type platelet differed significantly ($p = 0.0001$) from the mean percentage both for normal subjects (mean = 7%, range at $\pm$ 2 standard deviations, 0 to 20%) and for the post-treatment study on this patient ($p = 0.0005$).

Table II

Complement Studies of Case 2

Date	C3 (mg/100 ml; normal range: 100-200 mg/100 ml) (beta 1C/1A)	C4 (mg/100 ml; normal range: 18-53 mg/100 ml) (plasma)	Total Hemolytic Complement (units/ml; normal range: 80-170 units/ml)	Immune Complexes Titer*
9/12/78	61	10	85	1:32
10/12/78				1:8
12/6/78	154	17	105	not detected

*Detected by both monoclonal rheumatoid factor and Clq binding assays (15).

Circulating immune complexes and hypocomplementenia were detected when hyperviscosity syndrome was present, but they resolved when the syndrome was treated.

After treatment, the platelet differential count was dominated by 72% of the spread type platelet, which is associated with hyperactivity and is formed when cytoplasm spreads between adjacent extended pseudopodia. Statistical analysis showed that the percentage of the spread type platelet observed in the post-treatment study on this patient was significantly different ($p = 0.001$) both from normal subjects (normal mean = 8%, range $\pm$ 2 standard deviations, 0 to 20%) and from the pretreatment survey on this patient ($p = 0.009$).

Rebuck skin windows (Case 2)

Analysis of sequential coverslips revealed a normal pattern of emigration for polymorphonuclear neutrophils and mononuclear cells. Some polymorphonuclear neutrophils and macrophages contained round, homogeneously darkly staining cytoplasmic inclusions that varied in size and number from 10 to 12 per cell (Fig. 2C, 2D). These cytoplasmic inclusions were present on the six- and 12-hour coverslips predominantly where there was little evidence of degenerating polymorphonuclear neutrophils, thus suggesting phagocytosis of exudative immune complexes at the lesion site. Macrophages from the 24- and 36-hour coverslips contained large amounts of melanin pigment in addition to the larger cytoplasmic inclusions, which simulated Mott cells (Fig. 2A).

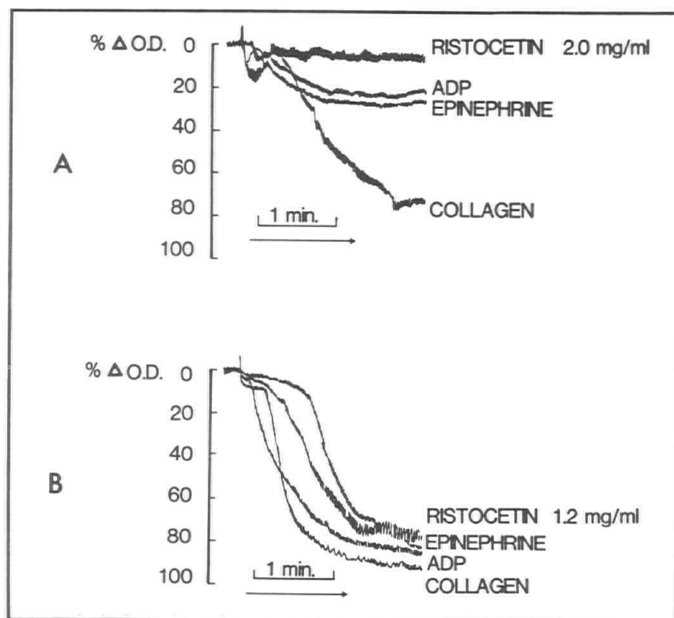

Fig. 3

Standard platelet aggregation by turbidometric determinations on Case 2: while there was clinical evidence of bleeding (A); and performed after plasmapheresis and one month of prednisone therapy when clinical evidence of bleeding was absent (B). In vitro platelet aggregation in the patient's blood was inhibited during pretreatment (A) and normal post-treatment (B).

Discussion

Hyperviscosity syndrome in rheumatoid arthritis

Both of our patients had seropositive rheumatoid arthritis and signs and symptoms of the hyperviscosity syndrome. Neither our patients nor others reported with hyperviscosity syndrome and rheumatoid arthritis (2-8) have developed multiple myeloma, a previously described occurrence with rheumatoid arthritis (21).

The first patient had numerous extra-articular manifestations of rheumatoid arthritis. Previously reported cases of rheumatoid arthritis complicated by hyperviscosity syndrome have shown nodules (3,5), Felty's syndrome (8,22), leg ulcers (2), and vasculitis characterized by nail fold infarcts and mesenteric arteritis (7). A hyperviscosity syndrome has been reported in patients with Sjogren's syndrome both with (8,22) and without (23-25) rheumatoid arthritis and associated with intermediate complexes (23) and IgA-IgG complexes (25).

In both of our patients we observed rouleaux formation and morphologic evidence of increased gamma globulin synthesis, including bone marrow plasmacytosis, Russell bodies, and circulating Mott cells. Rouleaux formation (6,23) as well as bone marrow plasmacytosis and lymphocytosis (3-5,7,8,23-25) have been found in other cases of hyperviscosity syndrome associated with connective tissue diseases. Generalized lymphadenopathy, perhaps another sign of lymphoid response to

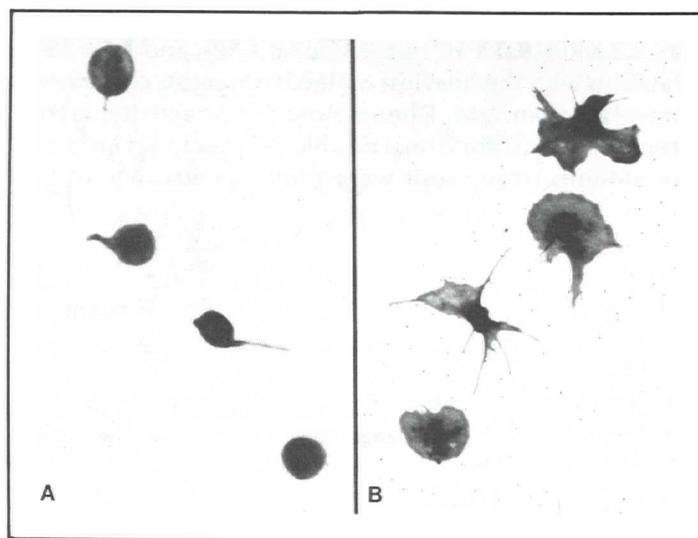

Fig. 4

Platelet morphology studied with transmission electron microscopy. A. The pretreatment platelet preparation from Case 2 showed >30% of the round type platelet, indicating that pseudopodia formation was inhibited. B. After treatment, the number of the spread type platelet was abnormally increased (X 4,300).

antigenic stimulus, has also been reported in patients with hyperviscosity and connective tissue disease (3,4,23,26). Previous studies have demonstrated that the bone marrow is the predominant source of immunoglobulin production in both normal individuals (27,28) and those with monoclonal gammopathy (29).

High molecular weight complexes

In the first patient there was no evidence of the presence of intermediate complexes either by comparing the difference between the gamma globulin and IgG concentrations (30) or by analytical ultracentrifugation. 22S protein, composed of 19S IgM rheumatoid factor and 7S IgG, has been detected without intermediate complexes in patients with rheumatoid arthritis without hyperviscosity syndrome (31-33) and correlates with high levels of rheumatoid factor and IgM (32). 22S protein was detected by analytical ultracentrifugation concommitant with intermediate complexes in some cases of hyperviscosity syndrome associated with connective tissue disorders (6,23,26), but not in others (2,5,24). In cases where they were present (6,23,26), the 22S complexes constituted a minor portion of the total protein.

In the second patient, IgM rheumatoid factor associated with intermediate and high molecular weight complexes contributed to the serum viscosity. The gel filtration done on plasma obtained before plasmapheresis (Fig. 7) showed that fractions containing IgM constituted most of the immunoglobulin. Dithiothreitol reduces 19S pentameric IgM into its 7S monomeric subunits. Reduction of the IgM with dithiothreitol resulted in a 44% reduction in plasma viscosity. The heaviest complexes contained more IgG than IgM and are likely to have included polymers of IgG rheumatoid factor. Evidence for IgG-IgM interaction included the double arc IgM and IgG precipitin lines, which disappeared in IgM-deleted serum, and the presence of 22S and 31S complexes that degraded into 6.2S and 16.55S peaks after acid treatment of the whole serum (Fig. 5). Although complexes of IgM rheumatoid factor interacting with intermediate IgG complexes were considered important

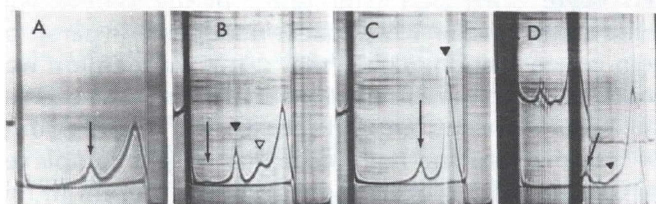

Fig. 5

Ultracentrifugal patterns of whole serum from Cases 1 and 2. A. Case 1 demonstrating 22S peak at 20 minutes (pH 7.3)· B. Case 2 serum after two days of plasmapheresis showing 31S (arrow), 22S (arrowhead), and 13S (open arrowhead) peaks at 22 minutes (pH 7.3)· C. Case 2 serum after two days of plasmapheresis showing 16S (arrow) and 6S (arrowhead) peaks at 22 minutes (pH 4.0)· D. Case 2 serum one month later during prednisone therapy showing 22S (arrow) peak and 9.7S (arrowhead) peak at 23 minutes (pH 7.3). Bar angle is 65° and sedimentation is from right to left.

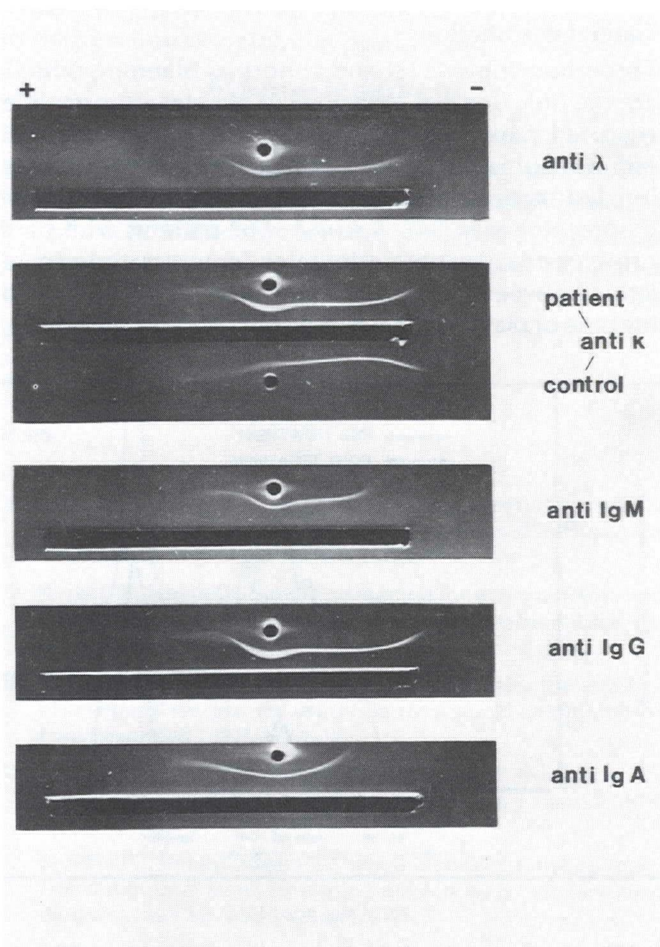

Fig. 6

Serum immunoelectrophoresis of pretreatment serum (Case 2) performed at room temperature. Double arc precipitin lines are present with all antisera except anti-IgA. Using the same antisera, there was no double arc precipitin line with control sera. One such example is shown with anti-K antisera.

in the hyperviscosity in previously reported cases (3), complexes heavier than 19S were not present on analytical ultracentrifugation, as they were in our case, even after plasmapheresis of 2,000 cc.

A mixed 19S-7S cryoglobulin (25) and one containing IgM, IgA, IgG, and C3 (7) were found in other cases of hyperviscosity syndrome and connective tissue disease. In the latter case, cryoprecipitate was found after gel filtration of the plasma in the fraction containing most of the IgM and rheumatoid factor activity, as in our second patient. Cryoglobulins were also detected in other cases of hyperviscosity syndrome and rheumatoid arthritis (2,8). Meltzer and Franklin detected the cryoglobulin in their patient only with dilution of the serum (2). They found that cryoprecipitation diminished when concentrations of macroglobulin exceeded 25 mg/ml.

Platelet dysfunction

Thrombocytopenia (3) and abnormal bleeding time (5) are the only findings indicative of platelet abnormalities reported previously in hyperviscosity syndrome due to either rheumatoid arthritis or Sjogren's syndrome. Platelet dysfunction is an important cause of bleeding in dysproteinemias (34). A study of 62 patients with paraproteinemia of various etiologies demonstrated a correlation between hemorrhage and either abnormal bleeding time or platelet adhesiveness (35). Platelet aggregation was not studied in these patients. In another study, platelet dysfunction, including ADP-induced aggregation, was found to depend on the paraprotein concentration (36). Abnormal platelet morphology as demonstrated by electron microscopy, bleeding time, and platelet factor III activity have been associated with the coating of platelets with macroglobulins in patients with Waldenstrom's macroglobulinemia (37).

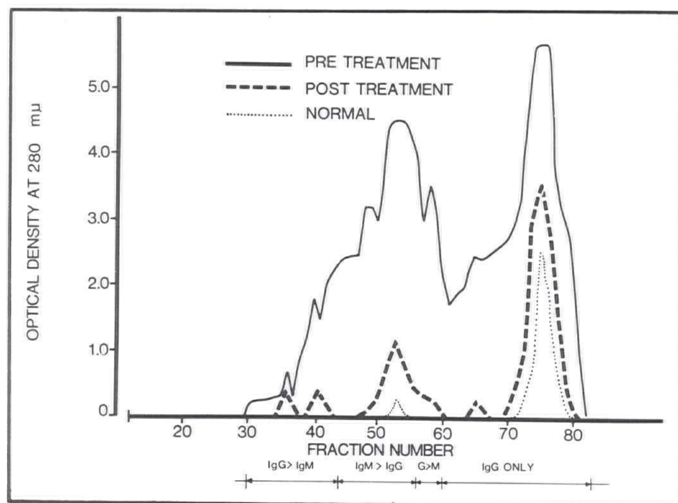

Fig. 7

Gel filtration through Bio-Gel A-15 done under identical conditions of sera from Case 2 and from normal. Post-treatment serum was obtained after one month of prednisone therapy. The relative proportion of immunoglobulin according to mg/dl is shown below the corresponding fraction numbers. Large amounts of abnormally present high molecular weight proteins (fractions 30-50) and intermediate molecular weight proteins (fractions 55-70) were present in the pretreatment sera.

When the platelet population from Case 2 was evaluated before treatment, the extrusion of pseudopodia by individual platelets was clearly inhibited. An abnormally increased percentage of the round type platelet has been observed when platelets were present in an environment which contained a high concentration of a large molecular weight substance such as the macroglobulin of Waldenstrom's macroglobulinemia (38). Reduction of the quantity of high molecular weight and intermediate complexes following plasmapheresis probably explains the increased ability of the platelets to extrude pseudopodia and exhibit cytoplasmic spreading between adjacent pseudopodia. Thus, the post-treatment platelet differential count for Case 2 was dominated by the spread type rather than the round type platelet. Also, in a comparative survey of the platelet reactivity of patients with various rheumatic diseases, we reported that 57% of patients with rheumatoid arthritis have hyperactive platelets when they are surveyed with our standardized in vitro method (39).

Cellular inclusions

Some patients with paraproteinemia exhibit decreased leukocyte emigration when tested by the Rebuck skin window technique, which does not depend on paraprotein concentration (35). In that study, no mention was made of cytoplasmic inclusions similar to those seen in our second patient. Since this patient had large amounts of intermediate and high molecular weight complexes in the serum, it is likely that they were present in the inflammatory exudative fluid induced by the skin abrasion of the skin window and were subsequently phagocytized by both emigrating polymorphonuclear cells and macrophages.

Intermediate and high molecular weight complexes (31) have been found in the sera of some rheumatoid arthritis patients without hyperviscosity syndrome. Under normal conditions, the mononuclear phagocytic system, especially the liver (40-42), is capable of removing high molecular weight complexes from the blood. However, once the cells are saturated, immune complex levels may increase rapidly in the presence of constant production (42,43). Such a sequence of events could account for the rapid increase in gamma globulin level (1.7 g%) in

five days seen in Case 1 (Fig. 1). Despite the presumed saturation of the mononuclear phagocytic system under conditions of excessive immune complex load, emigrating mononuclear cells seen in the six- and 12-hour skin windows of Case 2 contained numerous inclusion bodies.

Therapy

Plasmapheresis was effective in rapidly relieving the symptoms of the second patient and has been in others with hyperviscosity syndrome also (44). It is particularly effective when the syndrome is due to high molecular weight proteins because they remain predominantly in the intravascular compartment (44). Because the relationship between viscosity and paraprotein concentration as well as hematocrit is nonlinear (45), a small change in protein concentration can cause whole blood and serum viscosity to drop significantly. The response to plasmapheresis may also be partly due to improvement of mononuclear-phagocytic system function (46). However, patients with hyperviscosity syndrome and connective tissue disease have relapsed if steroids have not been continued after plasmapheresis (3-5,7). In these patients, low doses of prednisone have been effective in controlling the immunoglobulin.

Summary

We are reporting on two patients with rheumatoid arthritis and hyperviscosity syndrome. Case 2 provided an opportunity to study the bleeding diathesis. For the first time we have documented that the basis of the bleeding in the hyperviscosity syndrome can be due to the interference of intermediate and high molecular weight complexes with platelet aggregation as well as inhibition of platelet surface activation and adhesion.

A hyperviscosity syndrome associated with connective tissue disorders can be produced by different abnormal immunoglobulin complexes. The syndrome lacks characteristics that distinguish it from the hyperviscosity syndrome due to paraproteinemias. It can occur in patients with rheumatoid arthritis both with and without extra-articular manifestations or Sjogren's syndrome. Regardless of the type of immunoglobulin complex, plasmapheresis is indicated to relieve the symptoms of the hyperviscosity syndrome. Prednisone is recommended to depress immunoglobulin production.

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