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Brief Review

Hyperviscosity in plasma cell dyscrasias[1]

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Abstract. Plasma cell dyscrasias are characterized by a malignant clonal proliferation of plasma cells. Due to the excessive production of abnormal clonal gammaglobulins, or paraproteins, there are major hemorheologic changes in the circulation. As a result, clinical manifestations of the hyperviscosity syndrome become a major cause of morbidity and mortality. Pathogenic factors for the hyperviscosity are due both to increased plasma viscosity and to increased erythrocyte aggregation, leading to increased whole blood viscosity. These changes are dependent on the plasma concentration as well as the molecular size of the paraprotein with the threshold for onset of hyperviscosity for IgG >15 g/dl, for polymerized IgG_3 >4–5 g/dl, for IgA >10–11 g/dl; for polymerized IgA >6–7 g/dl and for IgM >3 g/dl. Correspondingly, the incidence of symptomatic hyperviscosity in Waldenstrom's macroglobulinemia is 10–30%, while that in IgG myeloma is 2–6%. Clinically, the syndrome has neurologic features of headache and dizziness, visual changes, renal failure, and cardiac failure from increased plasma volume. Thrombotic complications are frequent. Paradoxically, there can be bleeding complications due to impairment of platelet function. Removal of the paraprotein by plasma exchange (plasmapheresis) can effectively reduce the hyperviscosity. Long-term control of paraprotein production can be achieved by chemotherapy. The early recognition of the symptoms of hyperviscosity, confirmed by laboratory findings of increased paraproteins and of increased blood viscosity, is essential for the proper management of this group of disorders.

Keywords: Hyperviscosity, plasma cell dyscrasias, myeloma, Waldenstrom's macroglobulinemia, plasmapheresis

1. Introduction

Symptoms of hyperviscosity has been recognized in patients with macroglobulinemia since it was first described by Waldenstrom [4, 3]. This condition has also been recognized in other hematologic malignant disorders. Plasma cell dyscrasias are a group of clinical disorders characterized by clonal proliferation of plasma cells and the production of monoclonal proteins, known as paraproteins. These disorders and their associated paraproteins are shown in Table 1. They have in common two important features: the presence of one or more monoclonal immunoglobulins in the patient's blood, and the clinical complication of hyperviscosity syndrome. The latter is the result of a series of rheological changes caused by these abnormal immunoglobulins. In this article, a brief review on plasma cell dyscrasias and the associated rheological changes will be presented.

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2. Plasma cell dyscrasias

Among these, the most common is monoclonal gammopathy of undetermined significance (MGUS) [24]. This disorder is defined as a condition with a paraprotein level of <3 g/dl. It is found in 3% of the adult population. It is rarely complicated by hyperviscosity. The IgM-MGUS, estimated to be prevalent in 0.55% of the white population over age of 50 years, is associated with a high risk of progressing to Waldenstrom's macroglobulinema [33].

The second most common plasma cell dyscrasia is multiple myeloma. This disorder accounts for 13% of all hematologic cancers and has an incidence of 5.6 cases per 100,000 population in Western countries [23, 25, 30]. It is more common in the older population with median age of 70 years [20]. Improved treatment modalities including chemotherapy, biologic therapy and hematologic stem cell transplantation has increased the survival especially in those under age 50 years with the 10 year survival of 41% [7]. The paraproteins produced by the myeloma plasma cells are IgG in 60% cases, IgA in 20%, IgD in 2%, IgE <0.1% respectively. In rare instances, more than one monoclonal paraprotein may be present in the same patient. In 18% cases, the paraprotein may be only the light chain of the immunoglobulin. Less often are seen in cases of heavy chain of the immunoglobulin being the paraprotein.

Waldenstrom's macroglobulinemia is a plasma cell dyscrasia that is most commonly complicated by the hyperviscosity syndrome [12–15, 16]. It is classified as a lymphoplasmacytic lymphoma of B-lineage. The characteristic paraprotein produced by the lymphoplasmacytic tumor cells is a pentameric IgM. The age incidence increases sharply after the fourth decade of life, with 0.1 per million population with age >45 years and 36.3 per million with age >75 years [17]. Clinically, the patient may present with general symptoms of fatigue and "B symptoms" of fever and weight loss, with signs of enlarged lymph nodes and hepatosplenomegaly. Most manifest with symptoms of hyperviscosity, as discussed below. The former diagnostic criteria, based on paraprotein level have now been modified to include presence of lymphoplasmacytic tumor cells in the bone marrow [29].

In cryoglobulinemia, the paraprotein has the characteristic physical property of precipitation in cold temperature. It is seen in a number of diseases, including Waldenstrom's macroglobulinemia.

3. Hyperviscosity syndrome

This clinical spectrum of signs and symptoms known as hyperviscosity syndrome is the result of impaired blood flow especially in the microvasculature (Table 2). In early stages, as a consequence of decreased blood flow to the central nervous system, neurologic manifestations such as headache, dizziness, vertigo, deafness, and altered mentation are seen. This may progress to confusion and coma. Visual changes such as blurring of vision can result from retinal changes. They are characterized by retinal venous congestion with ophthalmologic appearance of engorged retinal veins often described as "link sausages". This process can lead to retinal vein thrombosis. Pulmonary blood flow obstruction can give rise to shortness of breath. Thromboembolic events involving both the arterial and venous circulation may complicate the more severe cases, with transient ischemic attack and stroke as neurologic complications, congestive heart failure and acute myocardial infarction as cardiac complications, and venous thrombosis, often occurring at unusual sites such as cerebral sinuses, and hepatic veins (known as Budd-Chiari syndrome).

The factors contributing to the increase in whole blood viscosity are shown in Fig. 2. They include not only the paraproteins, but also the red blood cells, platelets, coagulation pathways and the adhesive

molecules. Interactions among these factors lead to a complex pathogenetic picture in the hyperviscosity syndrome.

3.1. Role of plasma proteins

As whole blood has the rheological characteristics of a non-Newtonian fluid, the viscosity is determined by the hematocrit as well as by its protein contents. The effect of the protein on the viscosity is dependent on its molecular size. Among the normal plasma proteins, albumin with a low molecular size (65KD) exerts minimal effect, while fibrinogen having the largest molecular size (340KD) is an important determinant. Bell had demonstrated that the reduction of fibrinogen level by a defibrinating agent results in commensurate decrease in whole blood viscosity [6]. At the low level of 5 mg/dl, the viscosity of whole blood approaches that of a Newtonian fluid.

In the case of plasma cell dyscrasias, the abnormal proteins have a much larger molecular size and IgM paraprotein or IgA multimers have large the greatest effect. When the IgM concentration reaches 3 g/dl, the viscosity increases to 4–5 centipoise, at which level hyperviscosity symptoms would appear. For the other forms of paraproteins, monomeric IgG and IgA has smaller molecular sizes and the threshold levels for hyperviscosity is >10–15 mg/dl. In the case of multimeric IgG_3, the threshold level will be lower, around 4–5 g/dl.

Other plasma proteins that may cause microcirculatory obstruction are cryoglobulins. These have the characteristics of precipitating in the cold and redissolving on rewarming. Thus, circulatory impairment often take place in the cooler parts of the body, such as in the skin, where the occluded skin vessels appear as livideo reticularis, with the skin showing reticulated pattern of purple obstructed vessels.

3.2. Red blood cells

Though minimal red blood cell (RBC) aggregation involving two or three RBC does not result in microcirculatory impairment [5], larger aggregates are known to cause clinically significant vascular occlusion, ranging from hyperviscosity syndrome to catastrophic ischemia to multiple organs.

In plasma cell dyscrasias, the RBC aggregation can be demonstrated in patients' peripheral blood. If the blood is mounted on a cover slip preparation, the RBC can be seen to form aggregates known as rouleaux (French for rolls) (Fig. 1). These rouleaux can be dispersed by movement of the blood in between the slides. *In vitro* studies by Baskurt and Meiselman showed that the aggregate can be two dimensional or three dimensional. The various factors governing the aggregation is beyond the scope of this review and the reader is referred to their excellent description [5].

RBC aggregation is increased in other clinical disorders, either due to abnormalities of the plasma proteins or changes in the RBC. It has been recognized to be present in inflammatory conditions [2, 26] with the rheological factors being primarily increased plasma fibrinogen levels [35], and possibly due to other less studied changes in the red cell. The measurement of the erythrocyte sedimentation rate is commonly used clinically to show the severity of the inflammatory process. It can also be seen in hypercholesterolemia [36], and hyperlipoptoteinema [42]. In rare cases, abnormal fibrinogen can also produce excessive RBC aggregation resulting in vascular occlusive disease [21]. RBC abnormalities causing increased aggregation are seen in b-thalassemia [8], sickle cell disease [28], malaria [27] and autoimmune red cell disorders. In the latter group of diseases, there is presence of autoimmune immunoglobulins on the red cell surface. When these immunoglobulins react at cold temperature, they are known as cold hemagglutinins [14, 37]. In severe cases, large RBC aggregates may obstruct multiple blood vessels

Table 1
Common plasma cell dyscrasias and the associated paraproteins

Monoclonal gammopathy of undetermined significance (MGUS)	IgG
Multiple myeloma	IgG (60%), IgA (20%), IgD (2%), IgE (>0.1%), Light-chain (lambda or kappa) (18%) Heavy-chain (gamma, alpha, mu)
Waldenstrom's macroglobulinemia IgM	
Primary amyloidosis	(AL) amyloid IgG light chain
Cryoglobulinemia	IgG, IgM or immune complex

Table 2
The clinical spectrum of symptomatology in hyperviscosity syndrome

Mild–impaired microcirculation:
Neurologic : headache, dizziness and impaired mentation up to coma
Visual: blurring up to blindness
Pulmonary–shortness of breath
Severe- thromboembolic events:
CNS: transient ischemic attacks up to stroke
Heart: myocardial ischemia up to acute myocardial infarction
Peripheral arterial occlusion
Venous thromboembolism; often unusual sites
Budd-Chiari syndrome
Pulmonary embolism
Bleeding complications–impaired hemostatic function

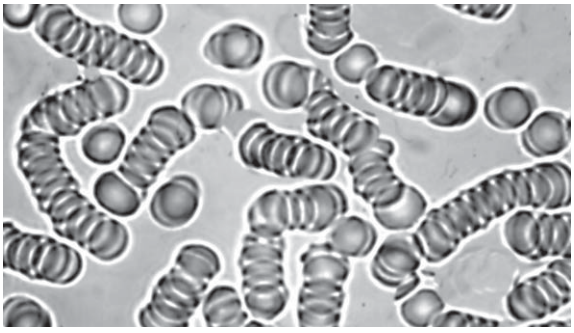

Fig. 1. RBC aggregates in the blood of a patient with IgM macroglobulins, appearing as rouleaux (as in stacks of coins).

resulting in catastrophic ischemia to multiple organ failure and to fatal outcome [1, 9, 38]. In unusual cases, increased blood viscosity can also be caused by therapeutic infusion of intravenous gammaglobulin leading to generalized impairment of the microcirculation. Severe RBC aggregation was observed in a patient with cold autoimmune hemolytic anemia, manifesting as extensive livideo reticularis following the misadventure of therapeutic infusion of intravenous gammaglobulin [22].

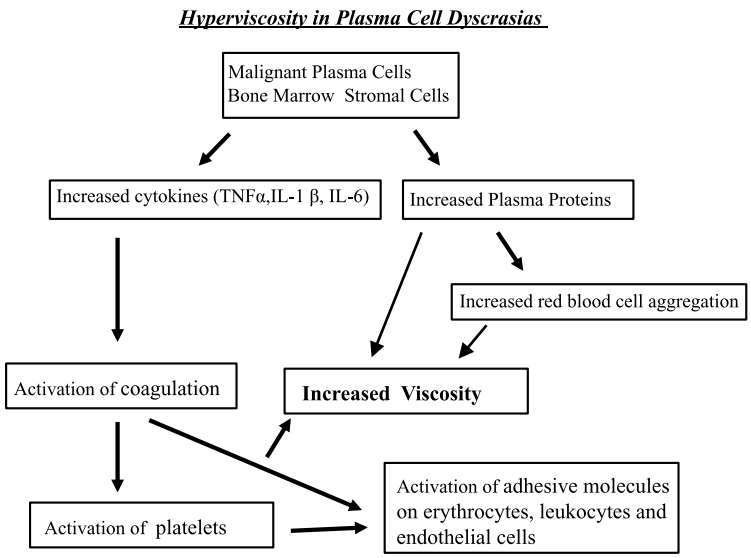

Fig. 2. Pathways leading to hyperviscosity in plasma cell dyscrasias.

4. Other adverse effects of paraproteins

4.1. Neuropathy

Deposition of the paraproteins in the myelin sheath of peripheral nerves results in neuropathic symptoms of pain and loss of sensory and motor function. This can affect up to 20% of patients with Waldenstrom's macroglobulinemia. Prolonged plasmapheresis (see below) may reverse some of the symptoms [3].

4.2. Increased risk of thrombotic complications

This can be the result of progression of the microcirculatory obstruction to extension of thrombosis in larger vessels. It can also be due to other adverse effects of the paraproteins. The various pathways are depicted in Fig. 2. These are increased expression of cytokines including TNFa, IL-1b, IL-6. These cytokines are mostly derived from the neoplastic plasma cells and from abnormal stromal cells in the myeloma bone marrow. TNFa enhances the expression of the procoagulant tissue factor in endothelial cells and monocytes. Initiation of the coagulation cascade will result in platelet activation, and further activation of adhesive molecules ICAM-1 (CD54), VCAM-1 (CD106), P-selectin (CD62P), E-selectin (CD62E); CD11b - receptor for ICAM-1 (CD54)on erythrocytes, leukocytes and endothelial cells.

4.3. Increased risk of bleeding complications

Other effects of the paraproteins are also present. There is increased in bleeding complications due to defect in the hemostatic function. First, the polymerization of fibrin monomers, an essential step in fibrin formation, is inhibited by the paraproteins [19]. Blood coagulation can also be impaired by the presence of heparin-like inhibitor [41]. Second, platelet aggregation is also impaired [18, 31, 32]. This is believed to be due to platelet binding of the paraprotein [11]. Acquired von Willebrand syndrome is also present in

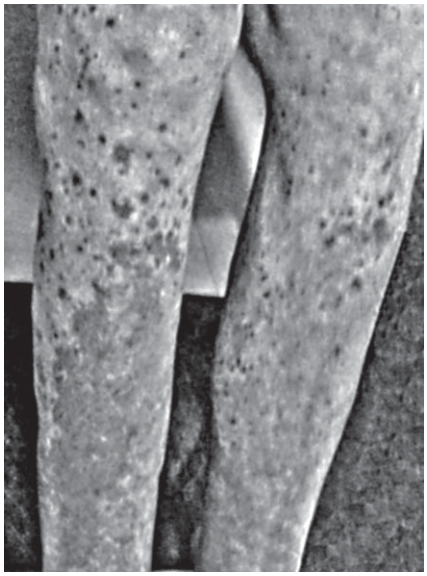

Fig. 3. Petechial hemorrhages in both lower limbs of a patient with high cryoglobulin level in her blood.

plasma cell dyscrasias [13]. Third, there is vascular deposition of certain paraproteins, such as amyloid, or cryoglobulin, in small vessels with endothelial injury and bleeding [34–40]. Figure 3 is an illustration of petechial hemorrhages in both thighs of a patient with high cryoglobulin level in her blood.

5. Diagnosis

5.1. Paraproteins

These can be diagnosed by measuring the immunoglobulins in blood, both quantitatively and qualitatively, the latter by using serum protein electrophoresis with immunofixation for the identification of the immune subtypes. In addition, the blood viscosity should be measured. In most clinical laboratories, serum viscosity is measured by a relatively simple method - that of the Oswald tube. The results are given in centipoise (cp). At 20°C, the viscosity of water is 1.0 cp, while that of normal serum is 1.4–1.8 cp. Symptoms of hyperviscosity rarely appear until the serum viscosity is >3.0 cp [10]. In Waldenstrom's macroglobulinemia, values of 5.0 cp or more are common.

Though measurement of whole blood viscosity gives a better picture of the *in vivo* pathology, the methods are cumbersome. The interpretation of values of whole blood viscosity has to take into consideration recognition that whole blood is a non-Newtonian fluid. As such, the hematocrit level of the tested sample is a strong determinant of the viscosity. Also the results are influence by the presence of any large RBC aggregates.

6. Management

The current standard of care is removal of the offending paraprotein by performing therapeutic plasma exchange. This is done by plasmapheresis [44]. This word is derived from plasma – apheresis (from the

Greek word "apheresis" meaning removal). Symptoms of hyperviscosity can be reversed as long as there are no thrombotic occlusions of the blood vessels. Thus, the therapeutic procedure should be carried out as soon as the diagnosis of hyperviscosity syndrome is made, to prevent further progression [4, 39].

The procedure involves withdrawing and pumping the blood from the patient into a conical centrifuge in the apheresis machine. The blood is then centrifuged to separate the plasma and cellular contents basing on their respective sedimentation coefficients. The undesired component is selectively removed and the remainder returned to the patient. In the case of removal of paraproteins, the volume of the plasma taken out will be replaced by 5% albumin or a mixture of an equal amount of albumin and 0.9% saline. Most plasmapheresis is carried out using the exchange of 1 to 1.5 times patient's plasma volume per procedure. Paraprotein of large molecular size, such as IgM, or IgA multimers, are distributed in the body with 70–80% in the intravascular compartment. Thus, one exchange can remove as much as 65% of these proteins in the body with the viscosity reduced by 20% or more. Generally one procedure per day is sufficient, except in severe cases, in which it is done twice a day. The frequency depends also on the rate of production of the protein by the abnormal plasma cells. The procedure is well tolerated with a low rate of adverse events. The complications are infection and hypocalcemia due to the citrate used as anticoagulant. Response to the reduction in whole blood viscosity is usually prompt, with the symptoms relieved after a few exchanges. The clinical outcome will depend on the control of the primary disease (the plasma cell dyscrasias) by chemotherapy.

7. Conclusions

Abnormal immunoglobulin in plasma cell dyscrasias may cause increase in whole blood viscosity. This can be symptomatic with manifestations of the hyperviscosity syndrome. If untreated, there can be serious consequences as generalized ischemia to multiple organs can happen. Symptoms vary, ranging from mild to severe and even fatal thromboembolism. In addition, the excessive paraproteins impair the hemostatic function leading to bleeding. This double hazard of both bleeding and thrombotic complications is often under-recognized clinically, especially in the early stages of the disease. It is thus important to diagnose the hyperviscosity as soon as symptoms of hyperviscosity appear to allow prompt reduction of the paraprotein levels by plasmapheresis and by treatment of the primary malignant condition.

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