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HYPERVISCOSITY SYNDROME

by Shirley D'Sa

CAUSE OF HYPERVISCOSITY SYNDROME

Patients with Waldenström's macroglobulinemia produce an IgM monoclonal protein, a fact that sets this disease apart from other types of non-Hodgkin lymphoma and provides a host of unique clinical challenges. The presence of IgM in the blood provides a 'tumor marker' that can be followed during the course of treatment to gauge the involvement of disease in the bone marrow. However, the presence of IgM within the blood stream may exert damaging effects on the functioning of the body due to its physical, chemical, or immunological properties.

Whole blood comprises red and white blood cells and platelets which are suspended in plasma, a tissue fluid that consists of water, important salts, and proteins, each of which has specific properties. The thickness or viscosity of the blood is determined by the number and size of the blood cells, as well as by the protein constituents of the plasma. An increase in the viscosity of the blood is an important complication encountered in Waldenström's macroglobulinemia. Increased viscosity results from the physical presence of the IgM paraprotein in the bloodstream. This protein is large, owing to its tendency to circulate in clusters of five, known as pentamers.

As the level of the IgM protein increases, so does the viscosity of the blood, but the relationship between the two is not linear. As a result, the viscosity of the blood may rise sharply even when there is only a modest elevation in the IgM level. As the viscosity rises, the flow of blood within the vessels slows down, reducing the delivery of oxygen and cellular nutrients to the tissues. The result is an impairment of tissue functions, and in this situation a variety of symptoms occur. This condition is termed the hyperviscosity syndrome (HVS). The incidence of HVS in Waldenström's macroglobulinemia is 10-30%. (1)



*IgM pentameric structure
(5 IgM molecules joined together)*

SYMPTOMS OF HVS

The symptoms of a raised blood viscosity result from sluggish flow of blood through the blood vessels. When occurring in the cerebral system, this may result in fuzzy-headedness, headaches, blurred vision, double vision, poor concentration and thinking, and, in severe cases, even reduced levels of consciousness. The risk of stroke is also higher under these circumstances.

Sluggish blood flow through the lungs may result in breathing difficulty. While such difficulty may initially occur on exertion, for example walking upstairs or uphill; when the blood flow is more severely impaired, breathing difficulty may happen even at rest.

Impaired flow through the coronary circulation may lead to chest pains due to angina in a patient prone to this problem. In patients with underlying heart problems, the development of ‘heart failure’ may occur, where the heart muscle struggles to pump effectively due to inadequate delivery of oxygen as a result of poor blood flow. The exertion of pumping more viscous blood through the circulation adds to the stress on the heart muscle. Patients with poor leg circulation characterized by pain when walking that improves with rest (such intermittent pain is known as claudication) may find this problem markedly worse in the setting of hyperviscosity.

All the above symptoms may be aggravated by the presence of anemia, which often co- exists with HVS since both problems are more common when the disease is burdensome within the body. Correction of HVS by plasmapheresis is usually needed in advance of a blood transfusion to avert a steep and dangerous rise in blood viscosity.

Another consequence of HVS may be a bleeding tendency resulting from the high shear force of blood flow in the smallest blood vessels or capillaries that causes them to rupture. Nosebleeds or bleeding in the gums, back of the eye (the retina), or the skin may result. It is most important to report any bleeding symptoms to your medical team so that appropriate assessments and investigations can be carried out.

DIAGNOSIS OF HVS

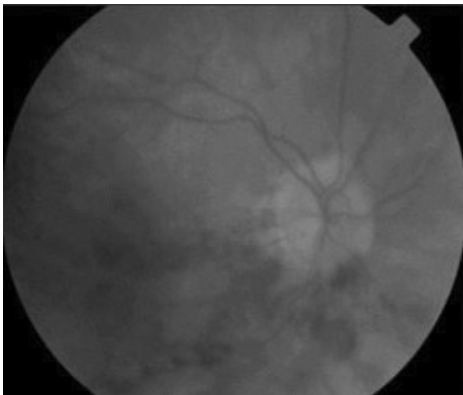


Photo of the retina showing hemorrhages secondary to HVS

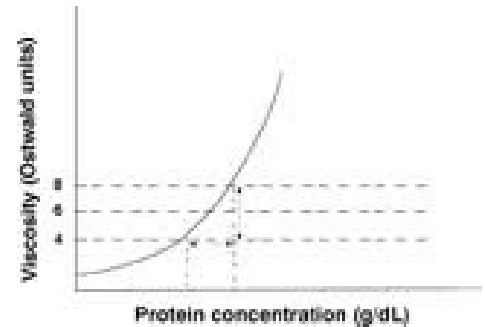
The symptoms of HVS can develop gradually as the IgM protein rises. As a result, the onset of symptoms may not be noticed until the situation is severe and may take both the patient and doctor by surprise. If the symptoms described above begin to develop, the possibility of HVS should be considered. (2) The possibility of HVS is greater when the M protein exceeds 4000 mg/dL. The onset of symptoms also depends on the condition of the blood vessel system. As people get older, their blood vessels become more rigid and may have a reduced diameter due to the depositing of fats such as cholesterol, akin to the “furring up” of a water pipe due to calcium deposition. A patient has an increased chance of developing the symptoms of HVS at lower levels of IgM if his blood vessels are rigid and have a fatty deposit.

The first assessment is a physical examination for signs of a tendency to bleed – bruises on the skin, blood blisters in the mouth or the back of the eye. It is important to view the retina at the back of the eye using an instrument known as an ophthalmoscope. Classical changes include sausage-shaped blood vessels and small bleeds on the retina. It is also important to assess the functioning of vital organs, primarily the heart and lungs.

Blood tests should be carried out to measure the levels of hemoglobin, the IgM protein, and plasma viscosity (PV), as well as the other routine tests of kidney and liver function. The PV is a test carried out in specialized laboratories. Normal plasma viscosity lies between 1.4 and 1.8 cp. As the IgM value

rises, the PV level tends to rise according to a logarithmic scale. Typically, a PV of 3.0 cp or less is not associated with symptoms. In most cases, subtle symptoms tend to arise when the PV reaches 4.0 cp. When the PV exceeds 5.0 cp, most, but not all, patients experience some symptoms, and 5.0 cp is regarded as being a critical level by most doctors for taking action to lower the plasma viscosity. However, symptoms can occur at a lower level of PV, and in this case should take precedence over the measured value of PV.

[Editor's note: Your laboratory may test serum viscosity (SV) rather than plasma viscosity. Whereas plasma is the complete liquid portion of the blood, serum is plasma without clotting factors. Serum viscosity and plasma viscosity are roughly equal, and the measurements discussed by Dr. D'Sa in this paragraph apply to serum viscosity as well.]



Relationship between serum viscosity and IgM level

TREATMENT OF HVS: PLASMAPHERESIS

Established hyperviscosity syndrome is a medical emergency that should be managed actively and promptly. Effective treatment relies on the physical removal of the IgM protein from the blood stream by a technique called plasma exchange or plasmapheresis.



Apheresis machine in action

Plasmapheresis consists of connecting the patient to an apheresis machine via two separate veins so that the blood can be circulated through the machine and the IgM protein physically removed via one vein before the blood plus albumin and saline is returned through the other vein. If the veins are not in good enough condition to be cannulated such that free flow of blood occurs, the insertion of a central venous catheter may be needed for the procedure. In the case of Waldenström's patients, because 70 to 80% of the IgM protein is contained within the intravascular space, a single plasmapheresis session can result in significant clinical improvement and a reduction in serum viscosity by 50% or more. (4)

In the acute setting, this procedure is carried out as an inpatient treatment, but it can also be performed as an outpatient procedure. Daily or alternate day single plasma volume exchanges are used initially until symptoms are relieved. Later, plasmapheresis may be repeated less frequently (such as once per week) as needed for control of symptoms. It is important for chemotherapy to be considered in parallel with the plasmapheresis so that the production of the IgM protein can be lowered definitively.

When should plasma exchange be used? This decision should be made on an individual-case basis, since the symptomatic threshold varies from patient to patient. Generally speaking, plasmapheresis is indicated for the following conditions:

- Symptomatic patients regardless of their plasma viscosity level
- Asymptomatic WM patients with plasma viscosity > 5.5 cp (this is an arbitrary cut-off used at our center)
- Patients who have had a previous heart attack or stroke or suffer from circulatory disorders such as poor circulation in the legs (such patients may need plasma exchange irrespective of the PV level)
- In patients with anemia that requires transfusion – prior plasmapheresis may be needed to ‘make room’ for the transfused blood

Special circumstances where plasmapheresis may be called for include the following:

- When surgery is required, for reasons unconnected to Waldenström’s. In some patients with a high IgM level who need surgery, I consider the need for plasmapheresis to aid healing and recovery post operatively, even if they are not otherwise receiving chemotherapy and are on a ‘watch and wait’ schedule. Plasmapheresis in this context improves the flow of blood at the site of the operation and is also likely to lower the risk of developing a deep vein thrombosis during or after surgery.
- In an emergency situation in which a patient is experiencing life-threatening effects of a raised blood viscosity and access to plasmapheresis is not immediately available. An improvement in blood flow may be achieved by a therapeutic venesection (removal of 250-300 mls of blood from a vein), with simultaneous replacement of normal saline or packed red cells, depending on the degree of anemia that is present. This maneuver can be carried out pending plasmapheresis to improve flow of blood to vital organs.
- The phenomenon of IgM flare. A rise in the level of IgM following treatment with rituximab is well recognised and does not represent failure of treatment. A flare is more likely to occur if rituximab is administered when the IgM level is 4000 mg/dl or above and may last several weeks. It is preferable to prevent this phenomenon in the first place by administering other chemotherapy agents that start to lower the IgM level before rituximab is commenced. However, if the IgM flare does occur, then some sessions of plasmapheresis may be needed to lower the PV in the short term until the treatment effect becomes established and the IgM level begins to decline.

COMPLICATIONS OF PLASMAPHERESIS

Plasmapheresis is generally well tolerated, but 12-40% of patients may experience complications during the procedure. The most commonly experienced complications are as follows:

- **Allergic reaction.** Allergic reactions are rare because few people react to infusions of albumin, the fluid that is administered as part of the exchange process following removal of the patient’s plasma. Should symptoms such as a rapid pulse rate, falling or rising blood pressure, skin rashes, or breathing difficulties occur during plasmapheresis, then the administration of an anti-histamine and corticosteroids is routinely carried out.

- **Viral infection.** Since albumin solution is a virally inactivated blood product, the chance of infection by a blood-borne virus is extremely small.
- **Excessive fluid in the circulatory system.** Owing to the fluid shifts that occur during plasmapheresis, an imbalance may occur, leading to fluid overload and breathlessness. This can be managed effectively by altering the flow dynamics on the apheresis machine or the administration of a diuretic to increase urine output. This balances out the fluid shifts and offloads the excessive fluid.
- **Mineral imbalance.** Similarly, imbalances in certain minerals, calcium and magnesium for example, may occur resulting in symptoms such as muscle cramps, twitching, and tetany (muscular spasms). This can be easily managed by the replacement of the mineral by intravenous infusion. The levels of these minerals and plasma proteins as well as kidney and liver function are closely monitored during and after the procedure.
- **Reduction in platelet count.** The platelet count may fall as a result of plasmapheresis due to removal of platelets as a side effect of the procedure. If platelets fall to a critical level, then a platelet transfusion may be needed. This is not a common occurrence; typically the reduction is modest, with spontaneous resolution over time.
- **Medication removed from the blood stream.** Some medications can be removed from the blood stream by plasmapheresis, especially if they are bound to plasma proteins. It is important to administer such drugs after completion of the procedure to avoid this problem.

CONCLUSION

The hyperviscosity syndrome is an important complication for some patients with Waldenström's macroglobulinemia. It can be easily identified if the symptoms and signs of the disorder are sought and effectively managed using plasmapheresis when indicated. Concomitant chemotherapy may also be important and is usually considered so that the root cause of the problem of IgM production by the lymphoma cells is addressed. Complications of plasmapheresis may occur but are not severe in most cases. The technique can dramatically reduce the symptoms and signs of HVS, reduce clinical risk, and improve wellbeing.

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Dr. Shirley D'Sa, M.D., F.R.C.P., F.R.C.Path, qualified in 1990 from St. George's Hospital Medical School, London. She trained in hematology at the Royal Marsden Hospital, Charing Cross Hospital, and University College Hospital (UCH), London, and was appointed as a consultant at UCH and Mount Vernon Cancer Centre (MVCC) in 2002.

Dr. D'Sa is a hematologist with a specialist interest in hematological malignancies, especially plasma cell disorders, working both at UCH, London, and the MVCC, Northwood. As Clinical Lead for Plasma Cell Disorders at MBVCC and Clinical Lead for Waldenström's Macroglobulinaemia at UCH, she does weekly specialist clinics in myeloma, lymphoma, and Waldenström's macroglobulinemia at UCH/MVCC. She also participates in regular Joint Paraprotein/Neuropathy Clinics with the peripheral nerve specialists at the National Hospital for Neurology and Neurosurgery, London.

Dr. D'Sa has worked with patients and colleagues to set up an not-for-profit organization called WMUK (www.wmuk.org.uk), which seeks to bring health professionals and patients closer together in the fight against the rare form of B-cell lymphoma, Waldenström's macroglobulinemia, including the organization of patient seminars for patients from across the UK and beyond. She is a member of the WM Guidelines Writing Group under the auspices of the British Committee for Standards in Haematology.

Guide to WM and LPL (2014) by Dr. D'Sa's is available as: [WMUK guides No2](#).

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