ROLE OF PLASMAPHERESIS IN MANAGEMENT OF WALDENSTRÖM'S MACROGLOBULINEMIA

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Therapeutic plasmapheresis (plasma exchange) is a procedure involving the separation of plasma from circulating blood cells in order to remove a disease substance. One major indication is to treat hyperviscosity syndrome (HVS), a common manifestation of Waldenström's macroglobulinemia (WM). HVS was described by Jan Waldenström in his original 1944 report of two patients with WM. The majority of patients with HVS have WM. Viscosity refers to resistance to flow or stickiness. Because IgM exists as a pentamer with molecular size of 925 kDa, this giant molecule can exert profound effects on blood cells and blood flow, especially when present in the high concentrations often found in WM patients. Patients with HVS have skin and mucosal bleeding, retinopathy with visual disturbances, and a variety of neurologic disorders (Stone & Bogen, Blood 119:2205-8, 2012). Heart failure and vascular manifestations are less common. HVS can be diagnosed from the physical examination by identifying characteristic retinal venous engorgement (sausaging) on funduscopic inspection. HVS can be accurately monitored with an Ostwald viscometer and is usually corrected by plasmapheresis. Normal viscosity measured with an Ostwald tube is 1.4-1.8 relative to water. When IgM levels rise above 3g/dL, the risk of HVS increases. HVS is unlikely unless serum viscosity is >4. Viscosity levels in HVS vary significantly **between** patients but correlate closely with signs and symptoms in the **same** patient (symptomatic threshold). The presence of cryoglobulinemia can result in a strikingly temperature-dependent elevation of serum viscosity. Accurate diagnosis of HVS from the eye exam enables appropriate therapy, that is, plasmapheresis, to be instituted promptly.

Plasmapheresis was first carried out for macroglobulinemia in the late 1950s and shown to reverse retinopathy and other clinical manifestations of HVS in most patients. This procedure remains effective short-term treatment for HVS because IgM is 80% intravascular and serum viscosity rises steeply with increasing IgM levels. A relatively small reduction in IgM concentration has a significant effect on lowering serum viscosity. Because bleeding is the most common sign of HVS, urgent plasmapheresis using a cell separator should be carried out for patients with visual symptoms to reduce the likelihood of blindness from retinal hemorrhages/retinal detachment. Plasmapheresis does not affect the underlying disease process and so chemotherapy is often begun concomitantly. Some WM patients can be managed predominately with plasmapheresis.

Plasma exchange may be helpful in patients with increased viscosity to prevent rituximab "flare". In patients with overt HVS, it is usually not necessary to plasmapherese down to normal viscosity to relieve symptoms. A potential exception may be patients who have autoantibody syndromes that produce neuropathy or other organ dysfunction. Plasmapheresis is generally safe and well-tolerated. The management of HVS in WM remains one of the most effective uses of this procedure.