Transfusion and Apheresis Science xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

The use of emergency apheresis in the management of plasma cell disorders

Sevgi Kalayoglu-Besisik*

Istanbul University, Istanbul Medical Faculty, Department of Internal Medicine, Division of Hematology, Therapeutic Apheresis Unit and Blood Bank, Istanbul, Turkey

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Plasmapheresis
Hyperviscosity
Plasma cell dyscrasias
Waldenstrom's macroglobulinemia
Myeloma

ABSTRACT

Hyperviscosity syndrome (HVS) develops most commonly in Waldenström's macroglobulinemia (WM) and multiple myeloma (MM). Plasmapheresis is the immediate therapy and very effective at relieving symptoms by removing paraprotein. The most commonly used replacement fluid is 4%–5% human albumin in physiologic saline. FFP may be used in patients with coagulation abnormalities. Plasmapheresis should be continued until acute symptoms abate. Hyperviscosity impairs the circulation in the retina and causes hemorrhages around the small retinal vessels. Early diagnosis and urgent plasmapheresis may reduce blindness caused by retinal hemorrhages and/or retinal detachment. In HCV related mixed cryoglobulinemias, plasmapheresis is indicated if rapidly evolving life-threatening disease with immunosuppressive agent exists. In non-infectious mixed cryoglobulinemia plasmapheresis is indicated when the disease manifestations are severe, as a second line option. In WM patients with hyperviscosity symptoms and IgM > 4 g/dL, preemptive plasmapheresis is recommended to prevent an IgM flare with rituximab. Certain IgG/A MGUS-associated neuropathy patients may benefit from plasmapheresis. For cast nephropathy (suspected or biopsy proven), plasmapheresis is recommended when the sFLC ≥ 500 mg/l and as early as possible (<1 month with kidney injury). Theoretically, extracorporeal removal alone, without efficient tumor killing, could not reduce sFLC due to high production by the tumor mass and rapid rebound between compartments.

Contents

* Corresponding author at: Istanbul University, Istanbul Medical Faculty, Department of Internal Medicine, Division of Hematology, Therapeutic Apheresis Unit and Blood Bank, Fatih Capa, 34390, İstanbul, Turkey.
E-mail address: sevgikalayoglu@istanbul.edu.tr

https://doi.org/10.1016/j.transci.2018.02.014
1473-0502/

1. Introduction

1.1. Paraproteinemias

The immunoglobulins produced by a B cell clone usually have an abnormal structure and are named, therefore, as paraprotein. "Para" is a prefix appearing in loanwords from Greek, with the meanings abnormal or defective [1]. An anomalous amount of paraproteins increases the blood viscosity. Polyclonal gammopathy induced hyperviscosity is relatively rare. Blood viscosity is influenced by a number of macrorheological parameters such as hematocrit, serum proteins, especially fibrinogen and globulins, and also microrheological parameters such as degree of aggregation and red blood cell deformability [2]. Clinically, the importance of blood viscosity is based on its oxygen delivery capacity especially at the capillary level [2].

For plasma viscosity, molecular weight and structure are major viscosity determining characteristics of proteins. Fibrinogen is a major plasma protein and has an important influence on viscosity. Albumin, a smaller and more globular molecule, had little effect [2].

1.2. Hyperviscosity syndrome in paraproteinemias

A significant increase in circulating paraproteins contributes to high serum viscosity, to vascular stasis and hypoperfusion which then lead to the clinical symptoms of hyperviscosity syndrome (HVS) [3,4]. HVS develops most commonly in Waldenström's macroglobulinemia (WM) and multiple myeloma (MM). It is important to remember that hypervolemia is a consistent feature of HVS [5] and iatrogenic HVS may develop from intravenous immunoglobulin administration, useful in selected myeloma patients with repeated bacterial infections [5].

The clinical presentation of HVS covers the triad of mucosal bleeding, visual changes, and neurologic symptoms. As viscosity rises, a nonlinear increase in shear stress in small blood vessels, particularly at low initial shear rates, produces damage to fragile vessel endothelium such as that of the eye and other mucosal surfaces. Constitutional symptoms and cardiorespiratory symptoms may also occur. Table 1 gives possible sign and symptoms of HVS [5]. The clinician should have a high index of suspicion for HVS in patients with unexplained altered mental status/coma or unexplained shortness of breath, especially in those with an underlying B cell clonal disorder. In suspected cases investigations should include blood cell count analysis with differential cell count, hemorrhagic diathesis tests, blood film which all should be followed by plasma viscosity measurement. A blood film characteristic related with hyperviscosity is rouleaux formation.

The diagnosis of HVS is established by high serum viscosity in a patient with characteristic clinical manifestations. Plasma viscosity is simple to measure, especially in capillary viscosimeters. Its normal value is 1.10–1.30 mPas at 37 °C and is independent of age and gender [3,4,5]. No exact diagnostic cut-off exists for hyperviscosity. Different patients will have symptoms at different values, which is related to the amount and stereochemical attributes of each patient's unique paraprotein [5]. HVS seldom occurs until relative serum viscosity is 4.0 and might be considerably higher in individual patients. However, the viscosity level at which the syndrome appears is generally reproducible within the same patient (symptomatic threshold).

HVS can be diagnosed from physical examination by identifying characteristic retinal venous engorgement ('sausaging') on funduscopic inspection. Hemorrhages, exudates, microaneurysms, papilledema, and an appearance indistinguishable from central retinal vein occlusion might be seen in later stages [5].

In general, symptomatic hyperviscosity is much more common in WM (10–30%) than it is in MM (2–6%). Symptoms of hyperviscosity usually appear when the serum viscosity reaches 4–5 cp, corresponding to a serum immunoglobulin M (IgM) level of at least 3 g/dL, an IgG level of 4 g/dL, and an IgA level of 6 g/dL [5].

1.3. Plasmapheresis in management of hyperviscosity syndrome

Accurate diagnosis of HVS from the eye exam enables appropriate therapy, that is, plasmapheresis, to be instituted promptly. Plasmapheresis is the immediate therapy of HVS and is very effective at reducing viscosity by removing paraprotein and relieving symptoms. Long-term management of HVS is directed at control of the underlying disease to prevent production of the monoclonal protein. So, chemotherapy is often begun concomitantly. However, some patients with WM can be managed predominately with plasmapheresis [6].

Plasmapheresis was first carried out for macroglobulinemia in the late 1950s [6,7]. Devices used to perform plasmapheresis can be divided into 2 broad categories, those that separate the plasma from the cellular components based on size and those that separate components based on density. Devices separating based on size use filters, whereas those separating by density use centrifugation. A replacement fluid is necessary to perform centrifugation based plasmapheresis and that is administered while the procedure is occurring. During each procedure the replacement fluid dilutes the intravascular abnormal protein concentration as it returned to the patient with the cellular components. So, removal of a substance

Table 1
Clinical presentation of hyperviscosity syndrome.

System	Sign and symptoms
Constitutional symptoms	fatigue, and anorexia
Central nervous system	headache, lethargy, vertigo, nystagmus, ataxia, deafness, paresthesias, convulsions, somnolence progressing to stupor and coma
Visual	blurred vision, diplopi, papilloedema, fundal hemorrhages, dilation of the retinal vessels, central retinal vein occlusion, retinal detachment
Cardiovascular system	high-output cardiac failure, shortness of breath, hypertension,
Hematological	dilutional anemia, abnormal bleeding (eg, bruising, mucosal bleeds; spontaneous gum bleeding, epistaxis, rectal bleeding, menorrhagia, persistent bleeding after minor procedures, thrombosis, leukocyte dysfunction (sepsis), cross match difficulties
Renal	renal failure, proximal renal tubular acidosis

Please cite this article in press as: Kalayoglu-Besisik S. The use of emergency apheresis in the management of plasma cell disorders. Transfus Apheresis Sci (2018), https://doi.org/10.1016/j.transci.2018.02.014