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Narrative Review

Clinical disorders responsible for plasma hyperviscosity and skin complications

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ABSTRACT

In this brief review, we have examined some clinical disorders which are associated to an altered hemorheological profile and at times accompanied by skin ulcers. This skin condition may be, in fact, observed in patients with primary plasma hyperviscosity such as multiple myeloma, Waldenstrom macroglobulinemia, cryoglobulinemia, cryofibrinogenemia, dysfibrinogenemia and connective tissue diseases. It must be underlined that the altered hemorheological pattern is not the only responsible for this skin complication but, as it worsens the microcirculatory flow, it contributes to determine the occurrence of the skin ulcers.

1. Introduction

The blood flow running through microvessels differs from that flowing through large vessels. These differences refer to the blood composition, the haemodynamics and specifically the blood viscosity. Rheological alterations play a prominent role in microcirculation than in large vessels haemodynamics. When a potentially ischemic condition emerges, some changes develop in microcirculation in relation to the diameter and the wall permeability of microvessel, the cell metabolism and the haemorheological profile.

Physiologically, the blood flow is influenced by blood velocity, vessel diameter, structure and blood viscosity. As for the blood viscosity, this is determined by the haematocrit, the plasma viscosity, and the red cell aggregation and deformability. Blood viscosity varies in relation with the shear rate. Results have clearly demonstrated that red cell deformability and plasma viscosity are very significant at high shear flow while red cell aggregation occurs at low shear flow.

In this paper we have examined, employing also unpublished personal data, several clinical disorders presenting a primary condition of plasma hyperviscosity and that may be associated in the clinical practice to skin lesions. The articles have been selected considering the following keywords: primary hyperviscosity syndrome; plasma cell disorders; cryoglobulinemia; cryofibrinogemia; dysfibrogenemia and tissue connective diseases. The lifespan of the research runs between the end of the 70 s until today.

2. Plasma hyperviscosity

An increased concentration of some plasmatic proteins may cause plasma hyperviscosity. The latter is due to the protein content, although the contribution of the different protein fractions significantly differs. It is known that albumin affects 36% of the difference between water and plasma viscosity (both Newtonian fluids), while its participation to the total of plasmatic proteins is 60%. Fibrinogen, instead, corresponds to only about 4% of the total plasmatic proteins, while its participation to plasma viscosity is about 22% under physiological conditions (this percentage changes significantly in case of cryofibrinogenemia or dysfibrinogenemia). The different contribution given by several protein fractions to the plasma viscosity is due to their molecular size and shape. In fact, the fibrinogen is more asymmetric in comparison with other proteins, as well as the globulins and the immunoglobulins contribute to plasma viscosity to a greater degree than albumin with reference to their higher molecular weight.

3. Plasma cell disorders

Patients with plasma hyperviscosity may be affected by skin ulcers; this hemorheological disorder is most often associated with plasma cell disorders. The latter are a heterogeneous group of blood diseases characterized by the detection of a monoclonal paraprotein in the serum or urine and/or the presence of monoclonal plasma cell in the bone marrow or, rarely, in other tissues [1].

Multiple myeloma (MM) is a plasma cell neoplasma characterized by the accumulation malignant plasma cells in the bone marrow producing a monoclonal paraprotein. The diagnosis of MM should be suspected observing the following signs and symptoms: unexplained anemia, hypercalcemia, acute renal failure or nephrotic syndrome, bone fractures or presence of bone lytic lesions on imaging evaluation,

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increased serum protein or presence of monoclonal paraprotein in serum or urine. A bone marrow aspirate and biopsy are key components to the diagnosis of MM [1].

To date, several papers, also recently have examined the hemorheological profile in MM patients [2–4]. One of our studies (submitted) carried out in a group of 24 MM patients has highlighted not only an increase in plasma viscosity (especially at low shear rate) and a decrease in haematocrit, but also a reduction in erythrocyte deformability. These data may be explained by the alteration of the lipid composition demonstrated in the erythrocyte membrane and in the plasma of MM patients [5,6]. Thus, it interferes with the membrane dynamic properties of the erythrocytes and then with their deformability. However, this alteration may be ascribable to the functional alteration of the desaturase and the elongase which have a role in the preservation of the lipid network of biological membranes. In addition, an alternative hypothesis may be explained by the presence of a paroxysmal nocturnal hemoglobinuria-like defect in the erythrocyte membrane of MM subjects [7–10]. This defect is characterized by an altered synthesis of the glycosylphosphatidylinositol, which is essential for the binding of some surface proteins, such as CD55 and CD59, to protect the erythrocytes from intravascular lysis. In MM patients, there may be the presence of skin ulcers [11,12].

Waldenstrom macroglobulinemia (WM) is a B-cell disorder characterized by the malignant store of clonally related B cells (lymphoplasmacytic and plasma cells) in the bone marrow and in other tissues. WM is a rare disease, the median age at diagnosis is 70 and about 20% of patients have a positive family history of haematological malignance in first-degree relatives. The most common symptoms are: fatigue/tiredness due to anemia, neurological disorders, symptoms of hyperviscosity (nosebleeds, blurred vision, headaches), lymphadenopathy, and hepatosplenomegalia. The diagnosis of WM is based on the findings of bone marrow biopsy, serum protein electrophoresis with immunofixation and the clinical picture [1]. Up to now, several papers have examined the behaviour of hemorheological profile in this clinical condition [13–17], showing a marked increase in serum and plasma viscosity associated mainly to a decrease in haematocrit. A hyperviscosity syndrome may develop in about 36% of patients with WM. In patients with WM have been described peripheral arterial perfusion disorders [18] and also skin ulcers [19,20]. To this extent, it must be underlined that cryoglobulins are found in about 37% of patients with WM. In our laboratory, we have examined (Table 1) a small group of WM patients observing an increase in whole-blood viscosity at high and low shear rates, an increase in plasma viscosity at high and low shear rates, a decrease in haematocrit and in erythrocyte deformability; this latter finding confirms those conducted by other authors who evaluated this hemorheological parameter in 12 WM patients using the same method [21].

Monoclocal gammopathy of undetermined significance (MGUS) is a clinically asymptomatic clonal plasma cell identified in 1% to 2% of general population. The diagnostic criteria for MGUS are: monoclonal immunoglobulin level < 3.0 g/dl, bone marrow plasma cells <10%, no bone lesions, no symptoms due to plasma cell dyscrasia, no related organ or tissue impairment, preserved levels of uninvolved immunoglobulins. Immunoglobulin G (IgG) MGUS is the most common type (70% of the cases), followed by IgM (15%) and IgA (12%). MGUS population includes 2% of 50 and 3% over 70 year olds. MUGS may develop in MM or, in some cases, disappear. An ongoing follow-up ranging 25 years, has shown a development in the lymphoproliferative disease in about 40% of subjects (about 1.5% of cases/year). A progression to MM was observed after that the monoclonal component had been stable for 20 years. Due to a lack of significant research [4,22] on the hemorheological profile in MGUS, we conducted in our laboratory, an hemorheological evaluation in a group of 21 MGUS subjects. By comparing normal controls to MGUS subjects, a significant increase in whole-blood viscosity (at high shear rate) and in plasma viscosity (at low shear rate) was observed (Table 2). In MGUS subjects the ratios between the high and low shear rate blood viscosity and Ht × 100, as well as the ratio between the low and high shear rate plasma viscosity have significantly increased. The alteration of the hemorheological pattern found in this clinical disorder might take part in the pathogenesis of a thromboembolic disease which results significantly higher in MGUS [23–26]. In MGUS subjects a decrease in erythrocyte deformability was also observed (Table 2). This finding may be perhaps explained by the presence of PNH-like defect observed in this clinical condition [8,27]. To date, PNH-like clones have been observed in several haematological disorders such as aplastic anemia, myelodysplastic syndromes and myeloproliferative disorders [28], and also in lymphoproliferative syndrome [29] and in acute leukemia [30].

4. Cryoglobulinemia

It is a clinical disorder in which the presence of plasma hyperviscosity may be associated with skin ulcers and in particular with leg ulcers. Cryoglobulinemia is due to the presence in the plasma or in the serum of one or more immunoglobulins which precipitate at a temperature below 37 °C and redissolve on rewarming. The composition of cryoglobulins is heterogeneous. Three basic types have been recognized according to the clonality and the type of immunoglobulins. Type I consists of monoclonal immunoglobulins, generally either IgM or IgG. Type II is an association of monoclonal IgM and polyclonal IgG. Type III is a mixture of polyclonal IgM and polyclonal IgG. Type II and III are described as mixed cryoglobulinemia because they consist of polyclonal IgG and IgM [31,32].

A percentage of 2% to 50% of patients affected by circulating cryoglobulins develop clinical symptoms. At the onset of the disease the most frequent symptoms (found in 80% of patients) are purpura, arthralgia and weakness. Other clinical lesions of cryoglobulinemia include the intermittent appearance of acral hemorrhagic necrosis, palpable purpura, lived reticularis, subungual hemorrhage, urticaria, Raynaud phenomenon, and erythema multiform-like lesions. Hyperviscosity syndrome develops especially in type I cryoglobulinemia and is uncommon in those with mixed cryoglobulinemia. Ferri et al. have demonstrated an alteration in plasma and serum viscosity and in cellular filtration index in a subject group with mixed cryoglobulinemia at 37

Table 1
Means ± S.D. and ranges of the haemorheological determinants in control subjects and patients with Waldenstrom macroglobulinemia.

	Control subjects	Patients with WM
BV 450 s^{-1} (mPa·s)	2.934 ± 0.393	3.800 ± 0.02
BV 0.51 s^{-1} (mPa·s)	24.18 ± 4.40	29.75 ± 3.06
PV 450 s^{-1} (mPa·s)	1.210 ± 0.065	1.687 ± 0.127
PV 0.51 s^{-1} (mPa·s)	2.657 ± 0.659	5.110 ± 2.217
Ht (%)	41.67 ± 3.51	32.67 ± 12.06
EI 60	45.13 ± 2.67	36.83 ± 1.48
EI 6	25.05 ± 2.39	16.55 ± 1.84

BV = Blood Viscosity; PV = Plasma Viscosity; Ht = Haematocrit; mPa = milliPascal; EI = Elongation Index. Statistical analysis not made because of the small number of cases (n = 3).

Table 2
Means ± S.D. and ranges of the haemorheological determinants in control subjects and MGUS subjects.

	Control subjects	MGUS subjects
BV 450 s^{-1} (mPa·s)	2.934 ± 0.393	3.353 ± 0.504**
BV 0.51 s^{-1} (mPa·s)	24.18 ± 4.40	26.80 ± 6.32
PV 450 s^{-1} (mPa·s)	1.210 ± 0.065	1.196 ± 0.140
PV 0.51 s^{-1} (mPa·s)	2.657 ± 0.659	4.429 ± 0.769***
Ht (%)	41.67 ± 3.51	39.24 ± 4.56
EI 60	45.13 ± 2.67	40.24 ± 2.93***
EI 6	25.05 ± 2.39	14.46 ± 3.19***

**p < 0.01 ***p < 0.001 vs Control Subjects (Student's *t*-test for unpaired data).
BV = Blood Viscosity; PV = Plasma Viscosity; Ht = Haematocrit; mPa = milliPascal; EI = Elongation Index.

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