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Skin Ulcers in Clinical Disorders Associated with Primary Plasma Hyperviscosity

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1. Abstract

1.1 Background: Several clinical disorders can be associated to primary plasma hyperviscosity with the appearance of skin ulcers.

1.2 Methods and conclusions: we have examined these clinical conditions that may be associated to primary plasma hyperviscosity and skin ulcers. In fact, these skin lesions are observed in patients with several diseases such as: multiple myeloma, Waldenström macroglobulinemia, cryoglobulinemia, cryofibrinogenemia, dysfibrinogenemia and connective tissue diseases.

2. Keywords: Erythrocyte Aggregation; Primary plasma hyperviscosity; Skin ulcers; Whole-blood viscosity

3. Introduction

Previously, some of us[1] have described skin complications deriving from plasma hyperviscosity, and the aim of the current article is to provide an indepth and updated analysis on such subject matter.

Hemoreological alterations play a pivotal role in microcirculation than in large vessels haemodynamics. Under physiological condition, blood flow is also influenced by blood viscosity; the latter is determined by haematocrit, plasma viscosity, and erythrocyte aggregation and deformability. Blood viscosity values depend on the shear rate. Clinical and experimental data have, in fact, demonstrated that red cell deformability and plasma viscosity are more significant at high shear flow, while red cell aggregation occurs at low shear flow.

This paper has considered clinical conditions presenting a primary plasma hyperviscosity, which may be associated to skin ulcers.

4. Considerations on Plasma Viscosity

The plasma proteins are all very large and have a high molecular wieght; the plasma proteins are usually subdivided according to their electrophoretic mobility. An increased concentration of some plasmatic proteins causes plasma hyperviscosity; the latter is due to the protein concentration, although the contribution of the different protein fractions significantly differs. The different contribution to 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, these contribute to plasma viscosity to a greater degree than albumin with reference to their higher molecular weight. Hemorheologically, the plasma proteins influence also the behaviour of red cell aggregation; the latter is a reversible process, with aggregates dispersed by mechanical or fluid flow forces, and then reforming when the forces are removed.

The non-protein content of plasma seems relatively less important as a determinant of rheological behaviour of plasma or blood. In fact, to date, there is no particular evidence indicating that triglycerides and cholesterol have a direct influence on blood and plasma viscosity.

Plasma viscosity has a remarkable inter-individual stability even if it changes in several clinical disorders. Plasma is considered a newtonian fluid, so its viscosity is assumed to not be dependent

on the shear rate. High shear rate-plasma viscosity is considered to be the true newtonian plasma viscosity. This parameter, as it is known, influences microvascular flow resistance which regulates the vascular tone and mantains a functional capillary density. In addition several clinical and experimental data have demonstrated that the incresead plasma viscosity stimulates the endothelial Nitric Oxide (NO) synthesis and reduce the vascular resistence. As it is known, NO is a gaseous messanger that reduces platelet adhesion and aggregation, diminishes leukocyte adhesion, regulates hemostasis and maintains the vascular smooth muscle in a non-proliferative status. To date plasma viscosity seems to be an independent risk factor for cardiovascular events.

An increase in primary plasma viscosity may be observed in several clinical disorders, below referred.

5.Connective Tissue Diseases

Patients with connective tissue diseases may suffer from skin ulcers, not only in systemic sclerosis, but also in rheumatoid arthritis, systemic lupus erythematosus, in ankylosing spondylitis, Sjogren's syndrome, in mixed connective tissue disease and in dermatomyositis [2-27].

In sistemic sclerosis the skin ulcers occur on the fingertips and on the dorsa of the interphalangeal or metacarpophalangeal joints, even several parts of the legs may be affected; the ulcers observed in systemic sclerosis were painful, slower to heal and refractary.

In rheumatoid arthritis the cause of leg ulcers is multifactorial; these ulcers have an angular configuration or an undulating border. Superficial Ulcerating Rheumatoid Necrobiosis (SURN) are bilateral over pretibial areas and are refractory to treatment. Adalimumab with methotrexate has shown promise.

In systemic lupus erythematosus skin ulcers are not that frequent; most skin ulcers are located over the malleolar, supramalleolar or pretibial areas. These ulcers are usually painful, sharply marginated,or punched out.

In anckilosing spondylitis the skin ulcers are less frequent; also in this connective tissue disease the pathogenesis of these leg ulcers is multifactorial and their presence can cause significant morbidity.

In Sjogren's syndrome the leg ulcers are not rare and these are associated to other disorders such as cryoglobulinemia, vasculitis, anti-cardolipin antobodies and Felty syndrome; these ulcers are quite painful and do not heal.

In Mixed Connective Tissue Disease (MCTD) are not rare chronic leg ulcers ; these ulcers may be refractory and need of complex treatments considering that MCTD is an overlap syndrome which puts toghether features of several connective tissue diseases associated with the presence of antbodes to UI-RNP.

In dermatomyositis and especially in Juvenile Dermatomyositis (JDM) it is possible the presence of skin ulcers has been described by many authors; these ulcers may regard the neck, the periombelical and gluteal area, the popliteal fossa and also the scrotom. Children with JDM and skin ulcers often show increased resistence to immunosuppresive treatment.

In all these connective tissue diseases, the rheological abnormality [28-39] and in particular the increase in plasma viscosity, attributed to the presence of the proteins of polyclonal origin, may play a role in the cardiovascular events, being one of the major causes of morbidity and mortality.

The increase in plasma viscosity may explain the alteration of the skin microvascular blood flow, even if, the effect of plasma viscosity might be mitigated by the increase in endothelial nitric oxide synthesis, reducing the vascular resistance. Plasma viscosity, in fact, controls the blood flow resistance, which regulates the vascular tone and preserves the functional capillary density; the alteration of the microcirculatory flow may contribute to the pathogenesis and deterioration of skin ulcers.

6. Qualitative Fibrinogen Alterations

6.1 Cryofibrinogenemia

It may be primary or secondary, and it is a rare disorder characterized by cryoprecipitation of the native fibrinogen in the plasma [40-43], which can cause thrombotic occlusions of the small to medium arteries. Cryofibrinogenemia, an unusual cause of non-healing skin ulcers, is a small-vessel occlusive condition that results from the plasma precipitation of cryofibrinogen [44]. Clinically, it is possible to distinguish patients with isolated or primary cryofibrinogenemia from those with associated cryoglobulinemia. Collagen diseases, infections and malignant diseases are less frequent in patients with isolated cryofibrinogenemia. Patients with primary cryofibrinogenemia suffered more frequently from recurrent and necrotic skin lesions. This clinical condition may cause a variety of skin manifestations (sensitivity to cold, purpura, livedo reticularis, cyanosis, erythema, uricaria, acral blisters), includingskin ulceration [45-54]. As regards, some authors [55] have examined 60 patients with cryofibrinogenemia of which 36 with essential cryofibrinogenemia and 24 with secondary cryofibrinogenemia observing a percentage of skin necrosis of 36.6% in the entire group; this percentage was instead of 44.4%

in the subgroup with essential cryofibrinogenemia and of 25.0 in which with seconadary cryofibrinogenemia. Also in the clinical course of an acute cerebrovascular event, a condition of primary cryofibrinogenema has been diagnosed [56].

Also in primary cryofibrinogenemia some authors have observed an alteration of the hemorheological profine [57].

Cryofibrinogenemia is a treatable and potentially reversible disease. The use of corticosteroids in association with low-dose aspirin is considered the specific treatment of moderate forms, even if stanozolol may result to be a possible alternative therapy. Immunosoppressive therapy, plasmapheresis, and/or intravenous fibrinolysis are useful for treating some severe forms of cryofibrinogenemia.

It must be highlighted that half of the patients with primary cryofibrinogenemia may develop lymphomas in successive years. This data has been obtained by Belizna et al [58] who carried out a research, through a multicenter follow-up study and the monitoring for 24 months, regarding a group of 23 patients with essential cryofibrinogenemia; 47% of cases initially diagnosed as essential cryofibrinogenemia were found to have a lymphoma. Other authors [59,60] have described an extensive auricular necrosis as symptom of cryofibrinogenia secondary to large B-cell limphoma.

Recently, some authors have described, in a 12-year retrospective study from a single center,the clinical aspects of children with cryofibrinogenemia;from this study it emerges that 5 children out of 8 showed skin necrosis or ulceration [61].

6.2Dysfibrinogenemias

These are clinical disorders characterised by high levels of plasma viscosity and erythrocyte aggregation [49]. Among the papers that have described the hemorheological profile in subjects with dysfibrinogenemia which that results more complete is the Mosdorf's paper [62]. This latter, in fact, has examined not only the hemorheological pattern of 14 patients with dysfibrinogenemia (of whom 12 are asymptomatics) but also which of 11 relatives demonstrating that plasma viscosity and erythrocyte aggregation were significantly higher in the patients than in their health relatives and in the control group. [63]have measured the erythrocyte aggregation in 12 patients with congenital dysfibrinogenemia observing thatthis hemoreological determinant was altered in 4 patients that had presentated a thrombotic disorder and was normal in those asymptomatics. While the papers of Mosdorf and Nguyen have regarded patients with essential dysfibrinogenemia, in the Kwaan's paper the marked increase of red cell aggregation responsible for digital ischemia and gangrene was observed in a case of acquired dysfibrinogenemia.

In our laboratory, examining a case with congenital dysfibrinogenemia, we found an increase in plasma viscosity at low shear rate and especially an increase in the ratio between plasma viscosity at low and high shear rate (unpublished data).

Dysfibrinogenemias are characterized by structural abnormalities in the fibrinogen molecule altering its functional properties [64-67]. The diagnosis of dysfibrinogenemia is related to a fibrinogen with abnormal structure or function. Generally, a dysfibrinogenemia may be suspected by discovering an abnormal thrombin time, with or without an abnormal reptilase time. Normal fibrinogen usually exhibits a 1:1 ratio of functional-immunological levels. The presence of a dysfibrinogenemia is suggested by a normal or increased immunologic level of fibrinogen with a lower functional level. Congenital dysfibrinogenemia is caused by heterozygosity for a mutation within any of the three fibrinogen chain genes. The incidence for congenital dysfibrinogenemia is not known due to the fact that the majority of patients appear to be asymptomatic, thus it may become unnoticed. To date, it has been estimated that 0.8% of patients with a clinical history of venous thromboembolism had dysfibrinogenemia. Acquired dysfibrinogenemia may be found in patients with autoimmune disorders, cancer, liver disease, or muliple myeloma [68]. This abnormality is most frequently detected in liver disease (cirrhosis or liver failure) and the increased sialic acid content that characterizes this clinical condition [69-71] leads to an enhanced negative charge that is likely responsable for the impairment of fibrinogen polymerization. The same alteration may be found in MM [72,73] as the monoclonal antibody may not specifically interfer with fibrin polimerization and morphology. Acquired disfibrinogenemia has been also associated with drug intake such as mithramicin [74].

Clinically, subjects with dysfibrinogenemia (congenital or not) are frequently asymptomatic (55%) even if some subjects will exhibit bleeding (25%), thrombotic complications (20%), such as skin necrosis, or both [75,76].

[75] have examined 101 patients with congenital dysfibrinogenemia presenting hemorrhagic and thrombotic events as well as complication of pregnancy and surgery; in this survey, they also observed that 10.9% and 13.9% had experienced major bleeding and thrombotic events, respectively.

7.Cryoglobulinemia

As it is known, it is a clinical disorder in which the existence of plasma hyperviscosity may be associated with skin ulcers and in particular with leg ulcers. Cryoglobulinemia is referable to the presence in the plasma or in the serum

of one or more immunoglobulins which precipitate at a temperature below 37 °C and redesolve 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 [77,78].

At the onset of the disease the most frequent symptoms 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.

Some authors have demonstrated a marked alteration in plasma and serum viscosity and in cellular filtration index in patients with mixed cryoglobulinemia at 37°C and at 25°C [79].

In our laboratory, examining a case with cryglobulinemia secondary to marginal lymphoma, we observed an increase in plama viscosity at low shear rate and especially an increase in the ratio between plasma viscosity at low and high shear rate associated with a decrease in haematocrit (unpublished data).

In many reports regarding mixed cryoglobulinemia, the presence of skin ulcers has been described [80-87]. At this regard, in a research effected by.[84] were examined 49 patients with symptomatic cryoglobulinemia in whom the skin involvement was present in the percentage of 81.6% altough the percentage of this association was not statistically different between $HCV^+$and HCV^-patients. [80]have, instead, examined 231 patients with mixed cryoglobulinemia recruited beteen 1972 and 2001. At the beginning of the follow-up the percentage of skin ulcers was of 11% while at the end of follow-up this percentage of 22% and therefore statistically significant. No statistical difference was instead observed between alive and deceased patients; in fact, in the alive patients the percentage of skin ulcers was of 10% while which of deceased patients was of 12%. The hemorheological alteration may influence and worsen skin ulcers through tissue ischemia even if the mixed cryoglobulinemia is a systemic vasculitis and the hemorheological impairment may favor the immunological damage in the vessel wall.

8. Plasma Cell Disorders

Plasma cell disorders are a heterogeneous groupof blooddiseases 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[88]. In the clinical practice, the principal plasma cell disorders are multiple myeloma and Waldenstrom macroglobulinemia.

8.1 Multiple myeloma

Multiple Myeloma (MM) is a neoplasm of plasma cells that accumulate in bone marrow leading to bone destruction and marrow failure, with a Monoclonal protein (M-protein) in serum and/or urine. This disease spans a clinical spectrum from asymptomatic to aggressive forms referable to deposition of abnormal immunoglobulin chains in different tissues.

The average age of MM patients is 62 for men (75%>70 year olds) and 61 for women (79%>70 year olds). The MM evolves from clinically silent pre-malignant stages denominated Monoclonal Gammopathy of Undetermined Significance (MGUS) and a middle clinical phenotype defined smoldering multiple myeloma.

Symptomatic myeloma is defined by the presence of end-organ damage (CRAB: hypercalcemia, renal insufficiency, anemia, bone lesions) in patients with a M-protein component and clonal bone marrow plasma cells. In several patients there is a cluster of clinical, laboratory, radiological and pathological findings. A M-protein is found in the serum or urine in about 97% of patients (IgG 50%, IgA 20%, light chain 20%, IgD, IgE, IgM and biclonal <10%); ~3% of cases are non-secretory. In 90% of MM patients there is a decrease in polyclonal Ig (<50% of normal). Other laboratory findings include hypercalcemia (20%), elevated creatinine (20-30%), hyperuricemia (>50%) and hypoalbuminemia (~15%). Radiographic studies show at initial diagnosis lytic lesions, osteoporosis or fractures in 70% of cases.

For the evaluation of the bone marrow plasma cell infiltration, bone marrow aspiration and biopsy is proposed to identify quantitative and/or qualitative abnormalities of plasma cells. The diagnosis of multiple myeloma requires 10% or more clonal plasma cells. A bone marrow aspirate and biopsy are key components to the diagnosis of MM.

To date several papers have also recently examined the hemorheological profile in MM patients[89-91]. One of our studies[6] has included a group of 24 MM patients highlighting not only an increase in plasma viscosity (especially at low shear rate) and a decrease in haematocrit, but also a reduction in erythrocyte deformability. This data may be explained by the alteration of the lipid composition demonstrated in the erythrocyte membrane andinthe plasma of MM patients[92,93]. In addition, an alternative hypothesis may be explained by the presence of a PNH-like defect in the erythrocyte membrane of MM subjects[94-97]. 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. The presence of skin and leg ulcers in MM patients has been described in many papers[98-101].

8.2 Waldenstrom Macroglobulinemia

Waldenstrom Macroglobulinemia (WM): Waldenstrom's macroglobulinemia is a rare low-grade malignancy that is observed in some patients with Lymphoplasmacytic Lymphoma (LPL) and is defined as LPL with bone morrow involvement and an IgM monoclonal gammopathy of any concentration. Familial clustering of B-cell neoplasms is well known and almost 20% of patients with WM. The presence of an IgM Monoclonal Gammopathy of Undetermined Significance (IgM-MGUS) is associated with an increased risk of developing WM on long-term follow-up. Indeed, IgM-MGUS is believed to represent a precursor to WM even if this haematological disorder is not always results preceded by IgM-MGUS which average risk of progression to WM is approxymately 1.5% per year. The classic pentad of WM is: (I) monoclonal protein on serum electrophoresis, (II) monoclonal protein confirmed to be IgM by immunofixation, (III) bone marrow evidence of LPL, (IV) evidence of hyperviscosity syndrome, (V) normocytic anaemia. Most patients present weakness and fatigue, usually related to the degree of anaemia; the majority of patients present an IgM serum paraprotein although others may have a different paraprotein or no paraprotein at all. A minority have both IgM and IgG or other paraproteins. Hyperviscosity occurs in 30% of patients. Other symptoms of WM are: neurological disorders, symptoms of hyperviscosity (nosebleeds, blurred vision, headaches), lymphadenopathy, and hepatosplenomegalia. Its diagnosis is based on the clinical picture and on findings of bone marrow biopsy, serum protein electrophoresis with immunofixation[88].

Up to now, several papers have examined the behaviour of hemorheological profile in this clinical condition[102-106], showing an increase in plasma and serum viscosity associated mainly to a decrease in haematocrit. WM patients may show peripheral arterial perfusion disorders[107] and also skin ulcers[108-112].

In our laboratory, we have examined[92] 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 carried out by other authors who evaluated this hemorheological parameter in 12 WM patients using the diffractometric method[113].

9. Conclusion

Several clinical conditions responsible for primary plasma hyperviscosity may be associated with skin ulcers. A significant impact of the hemorheological alteration on these ulcers has not been clearly demonstrated. However, a significant acceleration of the healing process of skin ulcers in all these clinical disorders associated with plasma hyperviscosity may be obtained through pharmacological treatment and plasma exchange. Such treatment improves significantly this hemorheological parameter and also the microcirculatory flow.

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