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CRYOFIBRINOGENEMIA – AN OFTEN-NEGLECTED RARE DISEASE: A CASE SERIES

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ABSTRACT – *Background:* Cryofibrinogenemia (CF) is a rare systemic condition characterized by reversible precipitation of circulating plasma components such as fibrinogen, fibrin, or fibronectin at cold temperatures that resuspend upon rewarming to body temperature.

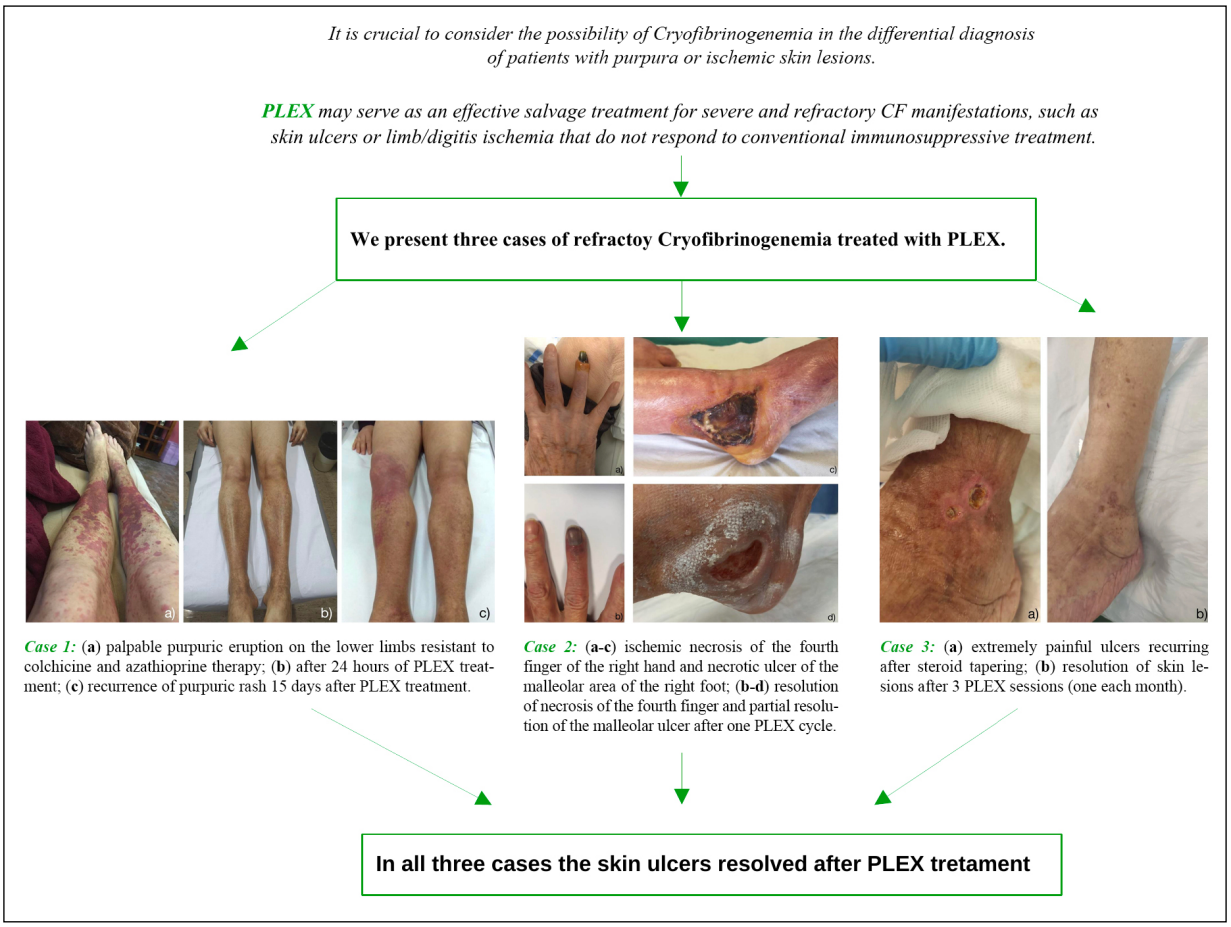
It is crucial to consider the possibility of CF in the differential diagnosis of patients with purpura or ischemic skin lesions. PLEX may serve as an effective salvage treatment for severe CF manifestations, such as refractory skin ulcers or limb digital ischemia that do not respond to conventional immunosuppressive treatment. Unfortunately, randomized controlled trials are lacking, and no guidelines exist. Our current knowledge is based on case reports and case series.

Case Series: We report a case series of three patients treated at IRCCS Policlinico San Matteo, Pavia, Italy, who presented with different clinical manifestations of CF refractory to conventional immunosuppressive therapies and were successfully treated with plasmapheresis (PLEX).

Conclusions: Management of CF includes glucocorticoids, whereas azathioprine, rituximab, cyclophosphamide, anticoagulants, and intravenous fibrinolysis have been reported to be effective in more severe cases. The proposed maintenance therapy for moderate disease is corticosteroids and low-dose aspirin or stanozolol. Treatment of refractory symptomatic CF remains challenging. Plasmapheresis (PLEX) has been reported in a few cases in the literature as a useful treatment for CF. The contribution of our cases highlights the importance of considering CF in the differential diagnosis among patients with purpura or ischemic skin lesions and PLEX as an effective salvage treatment for severe CF manifestations, such as refractory skin ulcers or limb/digital ischemia that do not respond to conventional immunosuppressive treatment.

KEYWORDS: Cryofibrinogenemia, Plasmapheresis, Corticosteroids, Skin ulcers, Purpura.

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Graphical Abstract. Treatment of refractory symptomatic Cryofibrinogenemia (CF) remains challenging: Plasmapheresis (PLEX) has been reported in a few cases in the literature as a useful treatment for severe, organ-threatening and therapy-refractory CF. Here, we present three cases from our experience where PLEX was necessary and permitted control of CF.

INTRODUCTION

Cryofibrinogenemia (CF) is a rare systemic condition characterized by reversible precipitation of circulating plasma components such as fibrinogen, fibrin, or fibronectin at cold temperatures that resuspend upon rewarming to body temperature[1,2]. The cryoprecipitate develops only in anticoagulated plasma but not in serum, which – unlike plasma – is devoid of clotting factors[3]. *In vivo*, cryofibrinogen deposits tend to form in the extremities, causing small- and medium-vessel occlusion in the acral regions, vasospasm, and hyperviscosity, leading to ischemic damage to downstream organs and tissues. CF is often asymptomatic. When clinically manifest, it may present with cold intolerance, acrocyanosis, Raynaud's phenomenon, livedo reticularis or microlivedo, purpura, skin ulcers up to extensive gangrene, superficial or deep vein thrombosis as well as arterial thrombosis, hemorrhage, arthralgias or myalgias, mononeuritis multiplex, and, less frequently, glomerulonephritis[1,4].

CF pathogenesis is largely unknown, and therapy indications are missing in the literature; idiopathic cases are defined as "primary (or essential) CF", while "secondary CF" indicates the presence of an underlying trigger such as neoplasia, infection, autoimmune diseases, cryoglobulinemia, and chronic inflammation. In some cases, monoclonal gammopathy of undetermined significance (MGUS)[5,6]. Given the lack of established therapeutic recommendations for CF, we aimed to explore the potential role of plasmapheresis (PLEX) in the management of refractory disease by describing three patients with distinct clinical manifestations who had failed conventional immunosuppressive therapies.

CASE REPORT

Case 1

A 44-year-old Caucasian woman, a former smoker with a history of arthromyalgia in her lower limbs for about one year, presented to our attention with pomphoid, non-puritic macular lesions in her upper limbs. She then developed a palpable purpuric eruption on the lower limbs gradually spreading up to her buttocks. Laboratory investigations showed lymphopenia, mild elevation of ESR and CRP, and hypergammaglobulinemia with a 12% immunoglobulin G (IgG) kappa (IgGk) monoclonal component. Cryoglobulin test showed only a modest serum deposit, whereas an abundant plasma cryoprecipitate appeared 48 hours later. Immunofixation showed monoclonal cryoglobulin type 1 IgGk (serum cryocrit 1%) and cryofibrinogen (plasma cryocrit 10%). The bone marrow biopsy revealed an inhomogeneous trilinear cellularity of 40%. High-dose prednisone and azathioprine were administered without partial amelioration of skin lesions. Azathioprine was thus replaced with colchicine; no significant improvement was observed. She underwent plasma exchange (PLEX) therapy with complete resolution of the skin rash within 24 hours, followed by reappearance after about two weeks (Figure 1). The patient underwent monthly PLEX to avoid the recurrence of skin lesions.

Case 2

A 77-year-old Caucasian female with a personal history of IgGk MGUS presented in 2012 with bilateral lower extremity dysesthesias, livedo reticularis, and necrosis of the left first toe requiring amputation. Blood tests revealed increased inflammatory markers, and the autoimmune panel, including antiphospholipid antibodies and cryoglobulins, was negative. Electroneurography revealed axonal sensorimotor polyneuropathy of the upper and lower limbs. She was diagnosed with cutaneous polyarteritis nodosa and treated with high-dose steroids with regression of the cutaneous manifestations. After a few years, she developed bilateral ulcers in the lower limbs and necrosis of the right fourth finger. She underwent an extensive laboratory workup, and a diagnosis of CF was confirmed. She was treated with high-dose prednisone and, subsequently, cyclophosphamide, followed by maintenance with azathioprine. Pain due to digital necrosis and leg ulcers persisted despite maximal opioid analgesic therapy; in fact, an indication for amputation had been placed. However, after a course of PLEX, the ischemic pain and leg ulcers disappeared (Figure 2), and the patient avoided amputation surgery.

Case 3

A 62-year-old Caucasian woman, an active smoker, without a remarkable medical history, developed bilateral dysesthesias of the four limbs. Electroneurography revealed axonal sensorimotor polyneuropathy of the upper and lower limbs. Infective, autoimmune and neoplastic causes of neuropathy were ruled out after a thorough investigation. Three months later, she developed Raynaud's phenomenon, livedo reticularis on the lower limbs, and painful skin ulcers on the knees and ankles. Laboratory studies showed neutrophilic

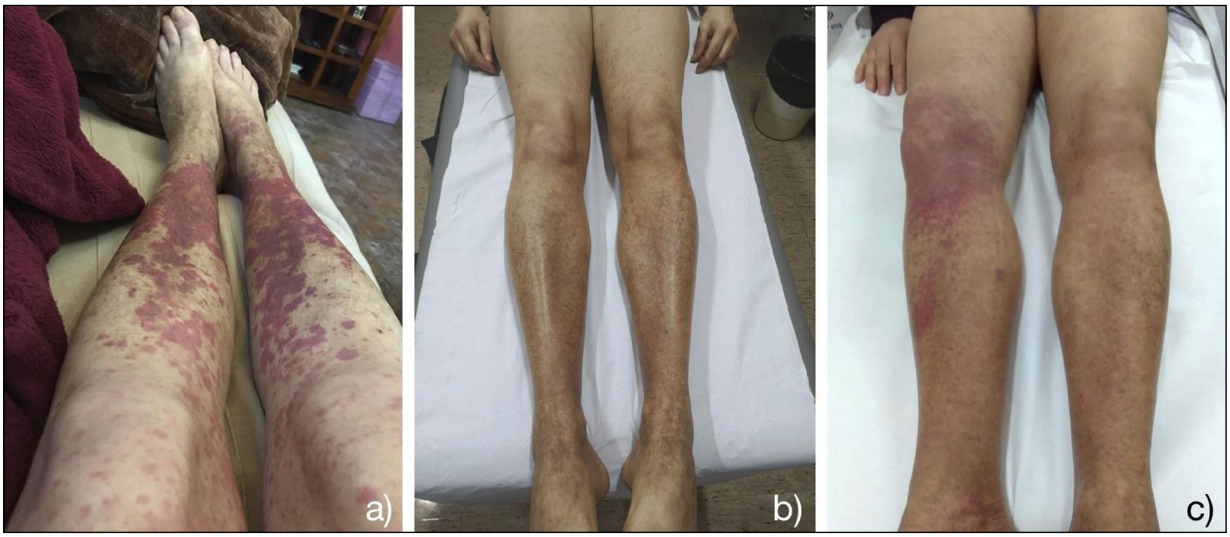


Figure 1. Patient in case 1: (**a**) palpable purpuric eruption on the lower limbs resistant to colchicine and azathioprine therapy; (**b**) after 24 hours of PLEX treatment; (**c**) recurrence of purpuric rash 15 days after PLEX treatment.



Figure 2. Patient in case 2: (**a-c**) ischemic necrosis of the fourth finger of the right hand and necrotic ulcer of the malleolar area of the right foot; (**b-d**) resolution of necrosis of the fourth finger and partial resolution of the malleolar ulcer after one PLEX cycle.

leukocytosis and increased inflammatory markers. Autoimmune tests were negative, except for positive rheumatoid factor and the presence of a cryoprecipitate. The deposit was analyzed and identified as cryofibrinogen. The patient started high-dose glucocorticoids with little improvement of the ulcers, which relapsed as soon as the steroid was tapered. She then underwent 3 cycles of PLEX, with consistent improvement of lower limb dysesthesia and almost complete resolution of the skin ulcers (Figure 3).

DISCUSSION

The clinical and therapeutic management of patients with refractory CF is complex. This may partly explain why only a few cases describing the use of apheresis in CF have been reported in the literature[6-8].

Case reports and retrospective case series have been published and dated more than ten years ago[7,8]. The evidence supporting refractory CF treatment with PLEX is limited, as reported in some reviews[5]. PLEX has been considered as the last therapeutic option in severe refractory or fulminant CF with severe organ involvement and limb amputation risk[9].

Consistent with the literature, we found delayed CF diagnosis in all three patients, primarily due to its misleading clinical presentation. CF differential diagnosis encompasses systemic vasculitis, especially ANCA-associated vasculitides, rheumatoid vasculitis, panarteritis nodosa, IgA vasculitis, cryoglobulinemia, antiphospholipid syndrome, as well as infection, neoplasia, purpura fulminans or other systemic autoimmune diseases[9]. While the cryofibrinogen test is easy to perform, it is not routinely administered to patients presenting with peripheral ischemic symptoms and is not usually performed in clinical labs.



Figure 3. Patient in case 3: (**a**) extremely painful ulcers recurring after steroid tapering; (**b**) resolution of skin lesions after 3 PLEX sessions (one each month).

Complications such as sepsis, disseminated thrombosis and bleeding, a poor prognosis, and refractory disease to steroids and immunosuppressive therapies in aggressive CF are described in the literature[9].

Moreover, systemic infection and sepsis are PEX contraindications.

Treatment of refractory symptomatic cryofibrinogenemia remains challenging; no guidelines or randomized controlled trials are reported in the literature, and CF remains a rare and orphan pathology.

All patients started high-dose glucocorticoids, resulting in partial improvement of their conditions. However, symptoms relapsed as soon as the steroid was tapered. First-line immunosuppressants such as azathioprine, rituximab and cyclophosphamide proved to be ineffective. Unal et al[10] reported the effectiveness of stanazolol in CF. Unfortunately, stanazolol was not an option for our patients, as it is not marketed in Italy.

PLEX emerged as the most effective therapy, promptly removing cryofibrinogen through filtration. All manifestations of CF in our patients, from mild to severe, responded readily to PLEX-mediated removal of cryofibrinogen, although symptoms usually recurred after a few weeks. Of particular note was the reduction of ischemic pain in the patient in case 2, which led to the cancellation of scheduled finger amputation surgery.

We believe our manuscript may contribute to the discussion of the importance of considering cryofibrinogenemia in the differential diagnosis in patients with purpura or ischemic skin lesions and PLEX as an effective salvage treatment for severe CF manifestations, such as refractory skin ulcers or limb/digitis ischemia that do not respond to conventional immunosuppressive treatment.

CONCLUSIONS

It is crucial to consider the possibility of CF in the differential diagnosis of patients with purpura or ischemic skin lesions. PLEX may serve as an effective salvage treatment for severe CF manifestations, such as refractory skin ulcers or limb digital ischemia that do not respond to conventional immunosuppressive treatment.

Conflict of Interest
The authors declare that they have no conflict of interest.

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Authors' Contributions
A. Biglia: conceptualization, data curation, formal analysis, supervision and project administration.
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M. Bozzola: conceptualization, data curation, supervision.
C. Iannone: conceptualization, data curation, supervision.
C.S. Cartia: conceptualization, data curation, supervision.
P. Delvino: conceptualization, data curation, supervision, resources, investigations.
F. Maggiore: conceptualization, data curation, supervision.
C.S. Chiricolo: conceptualization, data curation, supervision.
S. Sammorì: conceptualization, data curation, supervision.
L. Cavagna: conceptualization, data curation, supervision.
R.F. Caporali: conceptualization, data curation, supervision.
L.M. Castello: conceptualization, data curation, supervision.
M.R. Pellico: data curation, formal analysis, resources, writing original draft.

Ethics Approval
All data collection and image acquisition for this case report were conducted in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable Ethical Standards.

Informed Consent
Patients were informed of the scientific and clinical interest in their disease, as well as this anonymous publication, and provided written informed consent.

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