CASE REPORT

Cryofibrinogenaemia: not just skin deep

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SUMMARY

A Caucasian woman in her 60s with a history of rheumatoid arthritis presented to our institution complaining of skin ulceration. Her initial course was complicated by superinfection and sepsis until a diagnosis of cryofibrinogenaemia was finally established. Cryofibrinogenaemia remains as an under-recognised entity in part, because it can mimic other causes of skin ulcerations. In addition, its diagnosis can be challenging because of the particular handling techniques required of lab specimens. This case exemplifies some of the diagnostic and treatment challenges encountered while managing the patient with cryofibrinogenaemia.

BACKGROUND

Cryofibrinogenaemia has a prevalence of 3–13% in the general population and is an uncommon cause for palpable purpura.¹ It is largely underdiagnosed because of the special and stringent handling required of blood specimens prior to the running of laboratory testing. Cryofibrinogenaemia can either be primary or secondary to causes such as infection, malignancy, thrombosis and collagen vascular diseases. Therefore, when a patient presents with purpura or skin ulcerations, the possibility of cryofibrinogenaemia should be considered.

CASE PRESENTATION

A woman in her 60s presented to the hospital with a complaint of a disfiguring rash that had appeared 4 days back. Initially, it had started as lesions on the face but rapidly progressed to involve the arms, thighs and legs. She denied fever, haematuria, joint or muscle aches. She had not travelled recently, and did not recall exposure to any insects or ticks. Her medications were hydroxychloroquine, metformin, aspirin and hydrochlorothiazide, all of which we held during the admission. No new medications had been added and she denied any illicit drug use. She recalled a similar rash a few months back. During that time, she had stayed in the hospital for 1 week. A biopsy had demonstrated purpura with prominent intravascular fibrin thrombi formation (figure 1). Vasculitis or a leukocytoclastic process was not identified, and no eosinophils were found. Aspirin and hydroxychloroquine had been discontinued by then, as it was believed to be a drug reaction. She received oral prednisone and responded with complete recovery of the rash. Upon physical examination, large ulcerating irregular purpuric lesions were noted on the thighs and buttock areas. The lesions were not tender to palpation. No other physical findings were noted. Routine laboratory testing revealed white blood cell and platelet counts within the normal range. Extensive laboratory

testing including for D-dimer, fibrinogen and fibrin degradation products was not suggestive for a microangiopathic haemolytic process such as disseminated intravascular coagulopathy (DIC). A peripheral blood smear was also unremarkable. An extensive autoimmune workup was carried out including ANA, ANCA, C3 and C4 levels, cryoglobulins and was found unremarkable. A repeat biopsy was performed that demonstrated dermal oedema with fibrin thrombi within the superficial dermal vessels. No evidence of vasculitis, venulitis or calcification was seen upon histopathological investigations. She was given intravenous steroids for a week, but did not improve and subsequently left the hospital against medical advice before a diagnosis could be established.

Merely 2 days later, she returned to the emergency department hypotensive with a blood pressure of 90/55 mm Hg, tachycardia with a pulse of 150/min and a temperature of 39.5°C. She was observed to have widespread necrosis of the skin and resultant ulceration with surrounding cellulitis (figures 2 and 3). She was admitted to the intensive care unit for treatment of sepsis likely from secondary infection of her skin lesions. Broad spectrum intravenous antibiotics and vigorous hydration with intravenous fluids were promptly instituted. Plastic surgery performed debridement of the necrotic areas. She was deescalated to a regular in-patient ward as her general medical condition improved although the lesions persisted. Cryofibrinogenaemia was suspected and laboratory investigations confirmed the diagnosis. She was again treated with intravenous steroids but for lack of improvement, decided to seek treatment elsewhere. She again left the hospital AMA.

INVESTIGATIONS

An important aspect one must consider is the stringent handling of blood samples required when testing for cryofibrinogenaemia. False-negative and false-positive results are common. Blood should be collected in tubes containing oxalate, citrate or EDTA as an anticoagulant. After collection, the blood must be stored at 37°C until centrifuged. After centrifugation, the plasma should be stored at 4°C for 72 h. Cryofibrinogens develop between 24 and 72 h after cooling. If the sample is not centrifuged immediately, it must be kept at 37°C to prevent autoabsorption of cryofibrinogens by the red blood cells.¹

DIFFERENTIAL DIAGNOSIS

In the patient presenting with necrotic skin ulcerations, a number of potential causes should be considered in the light of clinical context. A history of

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Figure 1 Biopsy revealing occlusion of the small dermal vessels by fibrin and platelet thrombi.

cold exposure, for example, should prompt one to consider frostbite. This patient had a normal platelet count, therefore making thrombotic thrombocytopenic purpura, hemolytic uremic syndrome and heparin induced thrombocytopenia less likely a diagnosis in this setting. The presence of microangiopathic features on a blood smear along with an underlying infection or malignancy should prompt consideration of DIC. Additionally, warfarin can sometimes result in skin necrosis. Often, a biopsy plays a crucial role, particularly, in distinguishing cryofibrinogenaemia from other similar lesions like calciphylaxis or panniculitis, for example. In this instance, the biopsy demonstrated occlusion of the small dermal vessels by fibrin and platelet thrombi, a typical finding in cryofibrinogenaemia. Her diagnosis was likely secondary cryofibrinogenaemia related to her underlying rheumatoid arthritis.

Figure 3 Blackened areas of skin necrosis with surrounding cellulitis.

Figure 2 Patchy purpuric areas involving the thighs with irregular ulceration.

TREATMENT

This patient received intermittent prednisone during both admissions. She did not respond initially and her lesions progressed after she left AMA. In both instances, she left prematurely before treatment could be completed. Suggested treatments from various case reports include stanozolol, prednisone, azathioprine or chlorambucil. Intravenous streptokinase has been suggested for critical acute ischaemia owing to cryofibrinogenaemia.

OUTCOME AND FOLLOW-UP

The patient was contacted by telephone to inquire about her health. She informed us that she was being treated at another hospital and that her lesions had entirely recovered with continued prednisone. Also, it was discovered that she was being evaluated for an intra-abdominal malignancy based on suspicious incidental findings on outside imaging. It is worth noting here that some prospective studies have shown that close to half the patients with essential cryofibrinogenaemia later go on to develop a malignancy.²

DISCUSSION

Cryofibrinogenaemia offers a unique diagnostic challenge. In the asymptomatic population, it can reach prevalence rates close to 10%.³ Its diagnosis is important as it allows for institution of appropriate treatments. One reason it remains largely misdiagnosed is because of the stringent handling of laboratory samples required to make the correct interpretation. In addition, no specific criteria have been set, although proposed criteria include the importance of a compatible clinical presentation, the presence of cryofibrinogens, the absence of cryoglobulins and a skin biopsy showing the plugging of the superficial and deep blood vessels with thrombi.⁴

Two types of the diseases are essential and secondary cryofibrinogenaemia. Frequently associated disorders include malignancy, infection and connective tissue disorders. Connective tissue diseases, such as rheumatoid arthritis in this patient are strongly mentioned in the literature.^{5 6} These disorders may or may not be evident at the time of diagnosis of cryofibrinogenaemia, but can become clinically apparent later.⁷

The underlying pathogenesis of cryofibrinogenaemia, although uncertain, is often attributed to 'in situ' thrombosis mediated by circulating cryofibrinogens. The major components of cryofibrinogens include fibrinogen, fibrin and fibronectin

(also called cold-insoluble globulin).⁸ Other components include α_1 -antitrypsin and α_2 -macroglobulin, both of which can inhibit plasmin activity and thereby contribute to thrombus formation. Fibronectin within the cryofibrinogen complex may also interact with circulating immunoglobulins or immune complexes, and thus contribute an inflammatory component to its potentially prothrombotic nature.⁹ An immunological mechanism may play a significant role in the pathophysiology of cryofibrinogenaemia associated with malignancies, infections and connective tissue diseases.

Treatment is usually targeted at dissolving these thrombi and may include using fibrinolytic agents such as stanozolol, streptokinase or immunomodulators such as glucocorticoids and cytotoxic agents.^{10–11} Treatment of primary cryofibrinogenaemia is usually less satisfying, whereas treatment of secondary cryofibrinogenaemia consists of managing the underlying condition as well.^{1–12} Outcomes for such approaches, however, are limited to individual or small series of cases, making generalised statements regarding treatment difficult.

Learning points

- ▶ Review important differential diagnoses in the patient presenting with necrotic skin ulceration.
- ▶ Recognise cryofibrinogenaemia as an important cause of necrotic skin ulceration particularly in the setting of infection, autoimmune disease and malignancy.
- ▶ Understand the specific lab techniques required in diagnosing cryofibrinogenaemia.
- ▶ Review the various treatments used in cryofibrinogenaemia, such as prednisone and other immunosuppressants.

Competing interests None.

Patient consent Obtained.

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