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What's your diagnosis

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ARTICLE INFO

Article history:
Received 20 September 2013
Accepted 2 December 2013
Available online 21 February 2014

Keywords:
Cryofibrinogenemia
Gangrene
Thrombosis

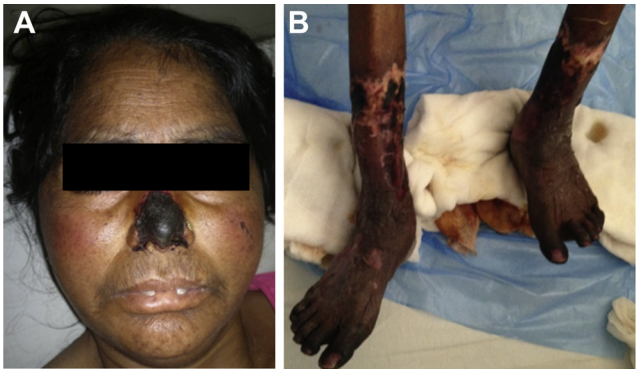

Fig. 1 – Gangrene of nose (A) and both legs (B) with clear line of demarcation.

1. Case report

A 55-year-old lady, daily laborer by occupation, presented to us at the height of winter with a 2 week history of bluish discoloration of tip of nose and ear and coldness of both feet, which progressed to black discoloration of both feet extending upto lower 1/3 rd of legs with blisters developing over these sites, over the next week. She was a chronic bidi smoker for 30 years, and had chronic obstructive airway disease (COAD) for past 7 years. She had no preceding fever, rash, oral ulcers, Raynaud's, limb weakness, visual symptoms, syncope, angina, claudication, palpitations, pedal edema. Examination revealed pulse 96/min, with both popliteals, posterior tibialis and dorsalis pedis absent. Blood pressure in right upper limb was 130/80 mmHg. She had gangrene of both feet extending to lower third of legs with blistering over these areas and clear line of demarcation (Fig. 1). There were also areas of gangrene over nose tips and helices of ears. Systemic examinations were normal except diffuse wheeze in both lung fields and a retained vaginal pessary. Complete blood count was as follows: Hb 10.4 g/dl, TLC 6800/mm^3, N72 L26 M2, Platelet 272000/mm^3. Liver and kidney function tests were normal. Chest X ray revealed prominent bronchovascular markings and ultrasound abdomen was normal. Echocardiography revealed moderate pulmonary arterial hypertension (RVSP 62 mmHg) possibly related to COAD, but no evidence of any thrombus or valvular lesion. Lower limb Doppler revealed thrombosis of both popliteal arteries. Sputum culture revealed presence of Klebsiella Pneumoniae (MDR) and Pseudomonas. Anti-HCV antibody was negative. C3 and C4 were normal, IgG ACLA was elevated (87.4 GPL) whereas IgM ACLA and anti β2GPI ab were negative.

What's your diagnosis?

Test for cryofibrinogen was positive. She was treated with daily dressing of wound, antibiotics, warfarin and vasodilators (Fig. 2).

2. Diagnosis

Cryofibrinogenemia, possibly precipitated by infection.

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http://dx.doi.org/10.1016/j.injr.2013.12.001

3. Discussion and review of literature

Cryofibrinogen is a plasma protein complex comprising predominantly fibrin, fibrinogen, fibronectin and factor VIII characteristically precipitating at 4 °C with re-dissolution at 37 °C, present in plasma but not in serum (thereby differentiating it from cryoglobulin).[1,2] It may be primary or essential in 50–60% cases, with secondary causes encompassing malignancy, infection, autoimmune diseases and miscellaneous causes like acute myocardial infarction and hypothyroidism[1,2]. Our patient had secondary cryofibrinogenemia possibly precipitated by infection. High plasma levels of protease inhibitors α1-anti trypsin and α2-macroglobulin have been proposed to inhibit the fibrinolytic agent plasmin, resulting in accumulation of cryofibrinogen which clots with thrombin leading to occlusion of small and medium arteries. Reflex vasospasm, hyperviscosity and vascular stasis result in additional vascular occlusion which may lead to tissue ischemia and gangrene if it involves end arteries.[3] Histopathologic changes described in skin, lung, muscle, nerve and kidney biopsies show a common occlusive hypereosinophilic deposit within blood vessel lumina and walls with variable lymphohistiocytic inflammatory infiltrate with or without accompanying granulomatous vasculitis component.[4] In addition, lung biopsies have demonstrated interstitial and intraalveolar red cell extravasation and hemosiderin deposition (immunofluorescence showing extensive homogenous and granular vascular staining for all immunoglobulin classes) and renal biopsies have shown additional hypereosinophilic mesangial and tubular deposits and glomerular basement membrane thickening.[4,5] Clinical features described are cutaneous manifestations (80.5–87%) - purpura, painful ulcerations, skin necrosis, Livedo and Raynaud's, vascular thrombosis (25–43%), arthralgia (11–34%), neuropathy (8–22%), nephritis (22%), myalgia (13%) and fever (9%).[1,2] Thrombosis has been noted in cutaneous vessels as well as in lower limb veins, pulmonary circulation and arteries.[1] Associated prothrombotic factors observed were lupus anticoagulant, anticardiolipin antibodies, hyperhomocystinemia, protein S deficiency, prothrombin gene mutations and methylene-tetrahydrofolate reductase gene mutations.[1] The diagnostic criteria for essential cryofibrinogenemia include essential evidences in the form of (i) appropriate clinical presentation, sudden onset of skin changes and constitutional symptoms, with or without thrombosis, bleeding, or exposure to cold (ii) presence of cryofibrinogen in plasma (iii) absence of cryoglobulins (iv) no secondary causes of cryofibrinogens and no evidence of other vasoocclusive disease; and supporting evidences (i) angiogram with abrupt occlusion of medium to small arteries (ii) typical skin biopsy findings: cryofibrinogen plugging vessels, leucocytoclastic vasculitis or dermal necrosis (iii) elevation of serum levels of α1-anti trypsin and α2-macroglobulin.[3] Therapeutic options described in literature include steroids (10–60 mg prednisolone daily) alone or in combination with azathioprine, chlorambucil or cyclophosphamide, oral or intravenous streptokinase, stanozolol, warfarin, plasmapheresis and cryofiltration apheresis.[1–3] Use of heparin has not been found beneficial.[3] Although nearly half of the patients respond to various therapies, around three-fourths of these relapse after a median period of 6 months.[2] In one series, 47% patients of essential cryofibrinogenemia developed lymphoma over a follow up period of 4 years.[2]

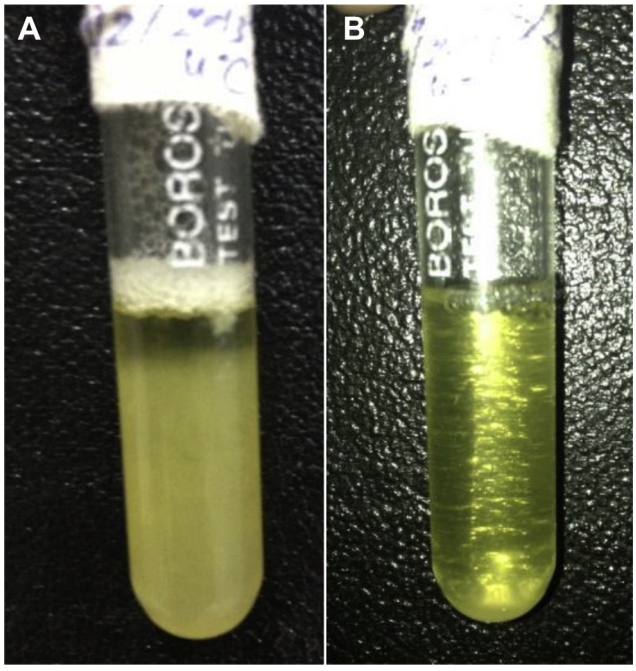

Fig. 2 – Demonstration of cryofibrinogen – Precipitation of cryofibrinogen at 4 °C in plasma (A) but not in serum (B).

4. Key conclusions

Cryofibrinogenemia remains an under-recognized cause of cutaneous ulcerations with gangrene and presence of these should herald prompt suspicion, especially during the winter months. Search for an associated systemic infection or malignancy (especially lymphoma) is mandatory both at diagnosis and on follow up.

Conflicts of interest

All authors have none to declare.

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Answers to Rheumatology Quiz

1d*, 2a**, 3b***, 4d, 5c†, 6b††, 7c§, 8d§§, 9c§§§, 10b¶

* The prevalence ratio of peripheral arterial disease in AS is 1.8 times that of age and sex matched controls; complete heart block occurs at the level of the AV node.

** On echocardiography, 37% of patients with SLE have been found to have a pericardial effusion.

*** Cardiac disease is usually less common in patient with ANCA positive vasculitides.

† Rhythm disturbances are commoner in patients with diffuse skin disease and their presence portends a poor prognosis.

†† Libman–Sacks endocarditis is associated with anti-phospholipid antibodies in 50% of cases.

§ Sarcoidosis may involve any part of the heart except the cardiac valves.

§§ Hydroxychloroquine toxicity can rarely cause a cardiomyopathy.

§§§ Focal myocardial fibrosis secondary to vasospasm is the hallmark cardiac lesion of PSS; this disease is not associated with accelerated atherosclerosis.

¶ CK – MB may be released from regenerating skeletal muscle fibers; troponin C and troponin T are also expressed in adult skeletal muscle.

Recommended reading for cardiovascular manifestations of rheumatic diseases

1. Roman MJ, Salmon JE. Cardiovascular manifestations of rheumatologic diseases. *Circulation*. 2007;116:2346–2355. Available at: http://circ.ahajournals.org/content/116/20/2346.full.pdf+html.

2. Owlia MB, Mostafavi Pour Manshadi SM, Naderi N. Cardiac manifestations of rheumatological conditions: a narrative review. *ISRN Rheumatol*. 2012;2012:463620. http://dx.doi.org/10.5402/2012/463620. Available at: http://downloads.hindawi.com/isrn/rheumatology/2012/463620.pdf.