with post-amputation mortality rates of 31 and 56% at 1 and 5 years, respectively—the highest reported worldwide [8]. Whether the high prevalence of TRAPS P46L in our population contributes to these high amputation and mortality rates and mortality remains to be established. In order to evaluate a definitive association, a patient case–control study, the WHy study (Wound Healing in Diabetes study), is being conducted in the Barbados population.

In vitro investigations have demonstrated that a critical control point in inflammatory resolution is the switch from pro- to anti-inflammatory cytokines [9]. Work in rodent models of diabetes has shown that TNF is overproduced in diabetic wounds and wound healing can be accelerated with anti-TNF treatment [3]. Persistence of TNF was also noted by our group in a skin blister model of wound healing in persons with diabetes [2].

This study serves to heighten the awareness of the rheumatologist to cross-specialty complications and to recommend intensive screening for risk factors of diabetic foot in patients with concomitant TRAPS TNF. The efficacy of anti-TNF biologics on the conventional symptoms of rheumatoid arthritis is debatable, seemingly variable and short-lived [10], with etanercept showing promising results and infliximab causing exacerbation [11]. However, if sustained TNF–α–TNFR interaction is involved in the poor wound healing seen in diabetic populations, then cautious pharmacological intervention with an anti-TNF, preferably etanercept, may offer some benefit in this unique category of patients. This may be especially relevant in those of West African descent in whom the allele frequency is high.

Rheumatology key message

- Intensive screening for risk factors of diabetic foot is advised in patients with concomitant TRAPS.

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Kim R. Quimby¹, Andre R. Greenidge¹, Anselm J. Hennis¹, David K. Harrison² and Robert Clive Landis¹

¹Edmund Cohen Laboratory for Vascular Research, Chronic Disease Research Centre, University of the West Indies, Barbados, West Indies and ²Regional Medical Physics Department, University Hospital of North Durham, Durham, UK.

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Correspondence to: R. Clive Landis, Edmund Cohen Laboratory for Vascular Research, Chronic Disease Research Centre, University of the West Indies, Barbados, West Indies B11115. E-mail: clive.landis@cavehill.uwi.edu

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Cryofibrinogenemia with vasculitis: a new overlap syndrome causing severe leg ulcers and digital necrosis in rheumatoid arthritis?

Sir, Vasculitis in the setting of RA occurs more frequently in long-standing disease (mean duration 13.6 years) and in patients with severe articular involvement [1]. Clinical features of rheumatoid vasculitis (RV) include leg ulcers, digital infarcts, scleritis, mononeuropathies and pauci-immune glomerulonephritis [1, 2]. The biological
hallmark of RV is depicted by very high levels of RF and elevated anti-CCP antibodies.

Cryofibrinogenaemia is defined by the presence of cold-precipitable proteins in the plasma [3, 4]. The cryoprecipitate consists of fibrinogen, fibrin, fibronectin and smaller amounts of various proteins. The distinction between cryofibrinogen and cryoglobulin arises from the fact that the former precipitates in cooled plasma and not in the serum [5]. Cryofibrinogenaemia can be classified as essential (primary) or secondary to drugs, various autoimmune diseases, infections or malignancy. Skin ulceration and thrombotic events are the main complications of cryofibrinogenaemia [6].

We hereby report the first case of a patient presenting intricate features of RV and cryofibrinogenaemia. A 57-year-old woman was admitted (July 2009) for polyarticular pain and sub-pyrexia (37.5°C). The patient had a 21-year history of seropositive RA and was currently being treated with AZA 100 mg/day and methylprednisolone 4 mg/day. Her past medical history included hypertension and macular degeneration. She had been previously treated with HCQ (1988–89), D-Pen (1990–92), MTX (1999–2006) and adalimumab (2006–08).

Physical examination revealed swelling and painful erythema of her right ankle. Blood analysis showed increased CRP (230 mg/l) and hyperleucocytosis. Cellulitis was suspected and i.v. amoxicillin–clavulanic acid was administered.

Two days later, the patient’s condition worsened with pyrexia of 39°C and the appearance of bullous lesions and ulcers over lateral and medial malleoli of both legs, as well as necrotic lesions of her feet soles (Fig. 1). CRP rose to 400 mg/l. Despite the administration of broad-spectrum antibiotics, there was no clinical improvement. Further investigations excluded an underlying infectious process. Administration of i.v. pulses of methylprednisolone (15 mg/kg body weight) during three consecutive days was followed by drastic clinical and biological improvements with a 50% CRP decrease over 2 days and the disappearance of skin oedema and erythema. Nevertheless, the patient developed necrosis of the digital pulps. In the following days, right episcleritis and lateral popliteal nerve palsy occurred. Additional blood analysis demonstrated the presence of very high titres of cryofibrinogen, while cryoglobulin, aCL and aPLs were negative. The cryoprecipitate was constituted exclusively of fibrinogen. Skin biopsy of the leg ulcers revealed vasculitis of medium size vessels, confirming the suspected diagnosis of RV associated with cryofibrinogenaemia. The addition of i.v. CYC 750 mg/m² every 3 weeks led to the healing of leg ulcers and normalization of both CRP and cryofibrinogen levels over a period of 3 months.

RV is a rare entity occurring in <5% of RA cases and its incidence is thought to have decreased markedly over the years [7]. Cutaneous involvement occurs in >90% of patients, characterized by deep skin ulcers found typically over lateral and medial malleoli. The vasculitic process can also entail nail-fold infarcts and gangrene [7]. In our patient, the association with cryofibrinogenaemia was suggested by the high titres of cryofibrinogen (>800 mg/dl). It should be stressed that such levels of cryofibrinogen are frequently associated with skin necrosis and digital infarction, whereas in asymptomatic cryofibrinogenaemia the amount of cryofibrinogen is <50 mg/dl [8].

Features of vasculitis involving medium size arteries have not been described in association with cryofibrinogenaemia. In our case, the typical clinical presentation encompassing perimalleolar skin lesions, digital necrosis, mononeuritis and episcleritis in association with compatible skin biopsies made the diagnosis of RV almost certain even without high titres of RF, anti-CCP antibodies or low C3. What is of most interest and should prompt further investigation is the role played by cryofibrinogenaemia (secondary to RA) in this particularly severe form of cutaneous and digital necrosis. Indeed, cryofibrinogenaemia is an entity whose underlying physiopathological processes are not very well understood. RV associated with cryofibrinogenaemia, involving digital infarcts and skin necrosis, has not been described. This might reflect the lack of awareness by physicians of the role of cryofibrinogen

**Fig. 1** Leg ulcers of the patient, as well as acrocyanosis, necrosis and digital infarcts.
as being responsible for skin and nail necrosis. Another feature suggesting the possible pivotal role of cryofibrinogenaemia in the skin process was the progressive decrease of the cryoprecipitate with treatment, together with clinical improvement.

RV should be kept in mind in any patient with long-standing RA, with multiple organ involvement and skin lesions. Furthermore, patients presenting with skin necrosis and digital infarcts should be screened for cryofibrinogenaemia. High titres of cryofibrinogen might play an aggravating role in the necrotizing skin process associated with RV and should be further investigated in prospective studies.

Rheumatology key message

Cryofibrinogen might be an additional factor responsible for severe necrotic lesions in RV.

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Muhammad S. Soyfoo1,*, Bruno Couturier2,* and Elie Cogan2

1Department of Rheumatology and 2Department of Internal Medicine, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium.

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Correspondence to: Muhammad S. Soyfoo, Department of Rheumatology, Erasme University Hospital, Université Libre de Bruxelles, 808 route de Lennik, B-1070 Brussels, Belgium. E-mail: msoyfoo@ulb.ac.be

*Muhammad S. Soyfoo and Bruno Couturier contributed equally to this work.

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