Tumor necrosis factor receptor-associated periodic syndrome P46L and bilateral amputation in diabetes

Sir, Tumor necrosis factor receptor (TNFR)-associated periodic syndrome (TRAPS) is an auto-inflammatory condition associated with defective TNFR mechanisms including retention of mutated TNFR in the endoplasmic reticulum, reduced activation-induced TNFR shedding and defective TNFR-induced signalling and apoptosis [1]. Persistently elevated levels of TNF-α have been reported in wounds of persons with diabetes [2], and wound repair in rodent models of diabetes was improved by anti-TNF administration [3].

This case engages the possibility that a cumulative effect of pro-inflammatory TNF contributes to impaired wound healing in diabetes and recommends intensive screening for risk factors of diabetic foot in patients with concomitant TRAPS. A 53-year-old black Barbadian female with Type 2 diabetes noticed a hyperpigmented area on her left hallux; 5 days later she was diagnosed with osteomyelitis that led to a below-knee amputation. Later, the patient developed a gangrenous right hallux that was subsequently amputated. Wound healing was marred by sloughing due to inflammation and infection, and further debridements were necessary before she could be discharged. During her hospital stay, persons with Type 2 diabetes-related lower limb complications were recruited and genotyped for the P46L (proline → leucine substitution at position 46 of the TNFRp55) mutation as part of a larger study. The patient was recruited with informed, signed consent and Ministry of Health/University of the West Indies Institutional Review Board approval in accordance with the principles of the Declaration of Helsinki as revised in 2000. It was noted that she was homozygous for the TRAPS 46L allele.

Subsequent examination revealed an obese female with a healed left below-knee amputation and right first metatarsal stump (Table 1). Glycosylated haemoglobin (HbA1C) (DCA 2000+; Bayer, Elkhart, IN, USA) was elevated at 10.3%. Neurothesiometry (Horwell Scientific Laboratory Supplies, Nottingham, UK) detected vibrations at 22 V on the pulp of the right second toe. The dorsalis pedis and posterior tibial pulses were neither palpated nor detected by Doppler (MD2/SD2; Huntleigh Healthcare, Cardiff, UK) and therefore the ankle–brachial index could not be calculated. The tissue oxygen saturation (SO2) was assessed by visible lightguide spectrophotometry (RM200 SO2 Monitor; Whitland Research, Whitland, UK). The degree of tissue hypoxia (the percentage of readings along the right leg with SO2 values of <15%) was 16.2%, indicating severe tissue hypoxia [4]. TNFR and TNF-α levels were determined by ELISA (R&D Systems, Minneapolis, MN, USA). Mean (s.d.) plasma TNFR was 117.5 (3.5) pg/ml (normal = 1077 pg/ml) [5]. Plasma TNF was 7.8 (0.4) pg/ml (normal = 0–7.3 pg/ml) [6]. Wound TNF was not measured.

The allele frequency of TRAPS P46L in a convenient sample of the Barbadian population was 9.5% (95% CI 5.8, 13.2; n = 120). In the black Barbadian segment, the allele frequency was 10.3% (95% CI 6.3, 14.3; n = 113). This was consistent with a reported allele frequency of 9.8% in a sub-Saharan cohort, some 30 times higher than in Caucasoid populations [7]. Included in this sample were the case’s mother and son who were found to be heterozygous and her half-brother (maternal) who was wild type.

The patient in this case did not report symptoms typical of periodic inflammatory syndromes. This is consistent with the view that P46L is a low-penetrance mutation [7]. However, her drastically reduced serum TNFR levels (117.5 pg/ml) corroborates the hallmark research which revealed that persons with TRAPS have lower levels of the shed TNFR [C88Y (402 pg/ml) and C33Y (899 pg/ml)] when compared with controls (1077 pg/ml) [5]. Her TNF-α levels (7.8 pg/ml) were higher than the normal range (0–7.3 pg/ml) and at the upper end of the range noted in TRAPS patients (0–8.9 pg/ml) [6]. Incident lower limb amputations in Barbadians with diabetes are among the highest reported in the literature.

### Table 1 Clinical and laboratory risk factors for foot ulceration in a patient with TRAPS P46L and diabetes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years/sex</td>
<td>53/female</td>
<td>Central obesity</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>1.08 (0.7)</td>
<td>Central obesity</td>
</tr>
<tr>
<td>HbA1C, %</td>
<td>10.3 (6.5)</td>
<td>Poor glycaemic control</td>
</tr>
<tr>
<td>Neurothesiometry, V</td>
<td>22 (4.3–6.9)</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Ankle–brachial index</td>
<td>Foot pulses not detectable</td>
<td>Peripheral artery disease</td>
</tr>
<tr>
<td>Degree of tissue hypoxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right leg, %</td>
<td>16.2</td>
<td>Severe tissue hypoxia</td>
</tr>
<tr>
<td>Right forearm (control), %</td>
<td>0</td>
<td>Tissue normoxia</td>
</tr>
<tr>
<td>TNFR, mean (s.d.), pg/ml</td>
<td>117.5 (3.5) (1077)</td>
<td>Low</td>
</tr>
<tr>
<td>TNF-α, mean (s.d.), pg/ml</td>
<td>7.8 (0.35) (0–7.3)</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

Values in parentheses indicate normal ranges.

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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 P46L. The efficacy of anti-TNF biologics on the conventional symptoms of TRAPS 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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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, mononeuritis multiplex and pauci-immune glomerulonephritis [1, 2]. The biological