Prevalence, serological features, response to treatment and outcome of critical peripheral ischaemia in a cohort of lupus patients

R. C. Jeffery¹, C. B. Narshi² and D. A. Isenberg²

Objective. This study addresses the issue of risk factors and management of critical peripheral ischaemia (CPI) and gangrene in SLE and proposes rituximab as a novel therapy.

Method. We conducted a retrospective study of 485 patients with SLE attending a UK tertiary referral centre, followed up over 27 yrs. Demographics, clinical features, serological features, treatment and outcome data were assessed.

Results. Seven out of 485 patients (1.4%) had evidence of gangrene or CPI with onset at any stage of SLE disease from presenting feature to 27 yrs after SLE onset, aPL and LAC were over-represented in the CPI patients. All had active SLE at the time of CPI. All seven were treated with intravenous (IV) epoprostenol infusion and aPL-positive patients were anti-coagulated. One patient failed to respond to this treatment and to IV calcitonin gene-related peptide but responded to B-cell depletion therapy using rituximab. Five out of the seven patients suffered digit loss with auto-amputation.

Conclusion. CPI is a rare but potentially devastating complication of SLE associated with aPL, LAC and active SLE. B-cell depletion therapy with rituximab may be an option in severe ischaemia not improving with IV epoprostenol.

Key words: Systemic lupus erythematosus, Anti-phospholipid syndrome, Digital ischaemia, Gangrene, Epoprostenol, Rituximab, B-cell depletion therapy.

Introduction

Critical peripheral ischaemia (CPI) is an uncommon but potentially devastating feature of SLE although little is published as to its prevalence and management. RP affects up to one-third of adult patients with SLE [1], and 10% of patients with childhood onset SLE [2].

A UK-based population study estimates critical limb ischaemia due to large- or small-vessel disease to occur in 0.1/1000 of the population per year and is associated with a high case fatality [3]. The pathogenesis is predominantly related to atherosclerosis, although thromboembolism also contributes. Traditional risk factors for acute vascular events contribute such as smoking, diabetes mellitus, hyperlipidaemia and hypertension. The pathogenesis of critical ischaemia in SLE is complex and multi-factorial, involving capillary and arteriolar vasospasm associated with RP, active large- and small-vessel vasculitis, micro-vascular thromboses and emboli associated with aPL and LAC, and accelerated atherosclerosis. The potential for recovery in a younger group of patients and disease reversibility in SLE should predict a better outcome if effective treatment is initiated early. A comparison of vascular disease between patients with APS who were more likely to be females, younger and with upper limb involvement, than an atherosclerosis group, showed better outcome [4]. An increased incidence of cardiovascular disease is recognized in SLE [5]. Predictors of peripheral vascular disease in SLE have been reported to be similar to those in non-SLE patients and include age, smoking, high CRP, acute coronary syndrome and long disease duration [6]. Endothelial function appears impaired in SLE with reduced responsiveness to dilatation with glyceryl trinitrate (GTN) compared with controls even in patients without additional cardiovascular risk factors [7].

We report the prevalence of CPI in a large cohort of patients with SLE in the UK, identify the risk factors for CPI and review the response to treatment and outcome.

Patients and methods

We reviewed the records of a cohort of 485 patients with SLE (444 females, 41 males, 62% Caucasian, 14% Afro-Carribbean, 11% Asian, 13% other, mean duration of disease 12.1 yrs) who attended our tertiary referral specialist centre in the UK between 1 January 1978 and 30 October 2007. All cases fulfilled four or more of the ACR 1997 revised criteria for SLE [8]. The prevalence of RP in this cohort was 28%. CPI was defined as rest pain and/or ulceration of digits/limbs, persistent pallor or dusky digits or necrotic digital lesions, of severity to warrant admission. The same assays were used for all patients as serum was saved from older patients and reassayed with newer aPL tests, retrospectively.

Results

CPI occurred in 7 out of 485 patients (1.4%) over the 28-yr follow-up period (Table 1). The majority were females (71%). The mean age of onset of disease in the affected patients was 22.1 yrs (range 15–39 yrs). CPI was found at any stage of SLE from presentation in two cases (Cases 1 and 4) to 24 yrs after disease onset (Case 7). The mean duration of disease before onset of critical ischaemia was 9.4 yrs with mean age at onset 31.5 yrs. Onset of critical ischaemia was unpredictable. It was associated with aPL/LAC positivity in four cases (Cases 1, 3, 5 and 7) and infection in two cases (Cases 2 and 7). An associated risk factor was not invariably, one patient (Case 4), with no associated aPL, had three episodes of critical ischaemia and gangrene of fingers and toes over a 23-yr course of disease. Although several patients were anti-RNP positive (Cases 2, 3 and 6), they had no features of SSc or myositis.

aPL and LAC were significantly over-represented in the group of SLE patients with CPI compared with the cohort as a whole; IgM and IgG-aPL 43%, LAC 43% in the affected group compared with IgM-aPL 9%, IgG-aPL 23% and LAC 14% in the SLE cohort as a whole. Two of the affected patients with aPL (Cases 1 and 7) were smokers and one patient (Case 1) subsequently developed deep venous thrombosis (DVT) and pulmonary embolism (PE); one lacking aPL (Case 6) was on the oral contraceptive pill (OCP) and...
<table>
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<tr>
<th>Patient details</th>
<th>Case 1</th>
<th>Case 2</th>
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<td><strong>Case 1</strong></td>
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<td>Renal (mesangial cell proliferation)</td>
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<td>Fits, depression, headache</td>
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<td>Anti-DNA-pos.</td>
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<td><strong>CPI extent and Gangrene of fingers outcome</strong></td>
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<td>20 yrs DD</td>
<td>0, 18 and 23 yrs DD</td>
<td>8 yrs DD</td>
<td>9 yrs DD</td>
<td>24 yrs DD</td>
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<td>Loss of finger tips</td>
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<td>Auto-amputation fingers and toes</td>
<td>First loss of finger/toe tips, second and third loss of finger tips</td>
<td>Full recovery</td>
<td>Full recovery</td>
<td>Left forefoot amputation</td>
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All patients ANCA, Anti-Sci-70/topoisomerase I, viral hepatitis and cryoglobulin negative. AAO, age at onset of SLE; DD, disease duration of SLE; pos., positive; neg., negative; DIC, disseminated intravascular coagulation.
one of the patients with LAC (Case 5) was on long-term rofecoxib (Vioxx, MSD, Hertfordshire, UK).

Case 4 presented with gangrene at onset of SLE. The three patients with renal involvement (Cases 1, 2 and 7) had no significant hypodubulinaemia preceding the thrombotic event. All cases had anti-double-stranded DNA antibodies (anti-dsDNA) except Case 7, and low C3 complement levels at the time of their critical ischaemia, indicating active SLE. All patients underwent Doppler arterial studies of the affected limbs. Only one patient (Case 3) had evidence of an arterial thrombosis that affected her palmar arteries bilaterally.

All seven patients were treated with continuous intravenous (IV) epoprostenol (Iloprost, GlaxoWellcome, Middlesex, UK) to the maximum tolerated dose for 3–5 weeks. Further treatment depended on the nature of the underlying precipitating cause. If aPL/LAC was present, the patient was anti-coagulated with IV heparin infusion (to maintain APTT ratio of 2) or subcutaneous low molecular weight heparin (enoxaparin 1 mg/kg twice daily) before conversion to long-term warfarin therapy. Any underlying sepsis was treated with appropriate antibiotics. Oral corticosteroid therapy was continued or increased for patients already on therapy (Cases 2, 3, 7 and 4—second and third episodes). Only Cases 5 and 6 made a full recovery without any digit loss. Neither had developed gangrene and both were aPL- and LAC-negative at the time of the ischaemic event.

Case 3 presented with severe gangrene of fingers and toes (Fig. 1), bilateral palmar artery thrombosises and aPL. She developed progressive ischaemia of her digits and necrotic ulcers on her elbows, mononeuritis multiplex with bilateral foot drop and peripheral sensory neuropathy of the feet. She was immunosuppressed with 750 mg IV cyclophosphamide and three consecutive pulses of 1 g IV methylprednisolone, followed by oral prednisolone 10 mg maintenance. Despite this, anti-coagulation with heparin and then warfarin, IV calcitonin gene-related peptide (CGRP) 0.6 µg/min for 3 h/day for the first 2 days (Clinalfa, Weil am Rhein, Germany) and then continuous IV epoprostenol infusion, she continued to develop new peripheral ischaemic lesions and spreading gangrene. An embolic source was excluded on echocardiography. This patient also had hypercholesterolaemia that was treated with an oral statin (atorvastatin, Parke-Davis, New York, USA). Ten days after admission she was treated with B-cell depletion using 1 g rituximab (Roche, Basel, Switzerland) infusion with 100 mg IV methylprednisolone, repeated at a 14-day interval, followed by a further infusion of 500 mg IV cyclophosphamide. Improvement of the ischaemia with no further progression was noted from 20 days after the first rituximab infusion (30 days from admission). Associated with improvement, her anti-dsDNA level by ELISA normalized (to 27 IU/ml from 112 pre-treatment), complement C3 normalized (to 1.31 g/l from 0.7) and IgG-aPL fell (to 16.6 GPLU from 36.6).

Over 2 yrs of follow-up her digits have slowly auto-amputated, left third, fourth and right fifth fingers to proximal phalynx, distal tips to nail bed of the other fingers and first, second toes and rest of the toes to metatarsal joint. Necrotic elbow ulcers healed without grafting. Her aPL level subsequently became negative; she has remained anti-dsDNA negative with a normal complement C3.

Discussion

aPL and LAC were over-represented in active SLE patients with CPI. In a large study of European patients a medium-high titre of IgG-aPL and anti-β2 glycoprotein I antibody was associated with thrombosis [9]. Although such titres of IgG-aPL were associated with four of our patients, macroscopic thrombosis was only detected in one. A large Mexican study of vasculitis in SLE found 0.9% of patients with active vasculitis developed digital necrosis with an association of aPL [10]. This is a similar prevalence to our finding in UK patients (1.4%). Three of our patients responded to treatment without the need for steroid immunosuppression. The prevalence of a first thrombosis in aPL-positive patients has been estimated at 1% per year and recurrent events in patients not on anti-coagulant therapy at 10–29% per year [11]. The role of long-term anti-coagulation of aPL-positive patients in this situation is uncertain. Of our patients, two of the three aPL/LAC-positive patients have been on long-term anti-coagulation—Case 1 (commenced subsequent to CPI for DVT/PE) and Case 3 (who had bilateral palmar artery thrombosis). The third case (Case 5) had only weak LAC positivity. Case 3 might be considered as catastrophic APS in association with SLE. However, prior to the onset of her illness she had no features suggestive of aPL and responded to treatment. LAC may be more specific than aPL as a predictor of thromboses in SLE [12], though whether this holds true with the more advanced aPL assays now available would require further study. With follow-up in our patients since initial CPI of 15.5 patient-yrs, only one patient (Case 4) has had recurrent episodes and he was aPL/LAC negative.

Dermatological features other than RP that may herald the risk of thrombosis in SLE- and aPL-positive patients include dermographia, acrocyanosis, urticaria, alopecia, livedo reticularis,
Evidence for treatment of peripheral ischaemia in autoimmune rheumatic disease (ARD) is limited and derives mainly from treatment of other causes of peripheral ischaemia such as atherosclerotic peripheral vascular disease, ischaemic diabetic ulcers and thromboangiitis obliterans, [17–20]. Studies in patients with ARD are mainly in those with SSc-related RP [21]. A now well-established treatment is epoprostenol (Iloprost), a synthetic analogue of prostacyclin, which has several therapeutic mechanisms of action; (i) vasodilatory effects [22], (ii) anti-thrombotic effects through reduction in platelet aggregation [23] and improved fibrinolytic activity [24], (iii) anti-inflammatory properties through reduced adhesion of leukocytes and expression of lymphocyte adhesion molecules on endothelial cells [25] and inhibition of pro-inflammatory cytokine production [26, 27].

Low-dose epoprostenol infusion (0.5 ng/kg/min) for RP in ARD, as used for our SLE patients, was as efficacious as higher dose treatment and associated with fewer side-effects [28]. A case series of vasculitic leg ulcers secondary to ARD showed improvement with epoprostenol therapy plus or minus immunosuppressive therapy [29] and there is evidence for benefit of epoprostenol in necrotic digital ischaemia secondary to APS [30]. More recently, a small retrospective analysis of paediatric patients with severe RP and digital ischaemia secondary to ARD (five with SLE) showed improved finger ulcer healing, pain relief, reduction in number of RP attacks and restoration of normal digital blood flow with epoprostenol infusion [31]. In all studies, epoprostenol is generally well tolerated.

Low-molecular weight heparin is used in combination with vasodilatory therapy in critical ischaemia for its anti-coagulant properties reducing micro-vascular thrombotic occlusions, and in addition may have actions attenuating inflammatory and regulating micro-circulatory responses to ischaemia [32].

The majority of cases of CPI associated with SLE that we describe, responded to treatment with IV epoprostenol +/- heparin +/- corticosteroid therapy. However, Case 3 continued to have progressive peripheral ischaemic lesions despite receiving such treatment. She also failed to improve with CGRP. This is an immunoreactive neuropetide present in digital perivascular neurons and produces powerful cutaneous micro-vascular dilatation [33, 34]. CGRP is found to be significantly reduced in the digital skin nerve fibres of patients with primary or secondary SSc-related RP compared with healthy controls. Following rituximab therapy, aPL levels have been shown to normalize and abrogation of thrombosis in APS occurs [35–37]. There is no published literature on the response of severe RP to B-cell depletion and our case is the first one to report on B-cell depletion therapy in severe progressive CPI associated with SLE, unresponsive to other therapy. A halt in progression of ischaemic lesions in our patient was associated with a fall in her anti-dsDNA and aPL, and normalization of her complement levels following effective B-cell depletion therapy with rituximab, given in combination with methylprednisolone and cyclophosphamide. We acknowledge that rituximab was only used in one case, but propose that B-cell depletion therapy could be used more generally, when IV epoprostenol is ineffective.

In conclusion, we report CPI in a large cohort of SLE patients identifying and reviewing risk factors, associated features and evidence for management. CPI is a rare but potentially devastating complication of SLE. We therefore urge that clinicians have a high index of suspicion, so that treatment can be instigated early. We found an association with RP, aPL, LAC, anti-RNP, active SLE and inter-current infection. We propose that B-cell depletion therapy with rituximab may be effective in severe ischaemia not improving with IV epoprostenol.

Disclosure statement: The authors have declared no conflicts of interest.

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