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SIR, Bosentan, an oral dual endothelin receptor antagonist, has been established in the treatment of primary and secondary pulmonary arterial hypertension [1, 2] and in the prevention of digital ulcers in SSc [3, 4]. Case reports indicate the improvement of RP [5], severe ischaemia secondary to lcSSc [6] and PAN [7].

We report on a 44-yr-old white female who has been diagnosed with subcutaneous lupus erythematosus (SCLE) for 8 yrs. The diagnosis of SCLE was initially based on the appearance of the typical non-scarring and non-fixed polycyclic skin lesions of SCLE and confirmed by skin biopsies showing immune deposits on the dermal-epidermal border. ANA, dsDNA, ANCA and complement factors were negative during the overseen timeframe of 8 yrs. Screening for organ involvement was done on a regular basis as well as high doses of prednisolone, especially because of the liver parameters stayed in normal ranges after bosentan had been started. Repeated oscillography (Fig. 1b) documented a marked improvement of blood flow in the lower extremities. A control MRA 3 months after bosentan had been initiated showed normal blood flow in the formerly obstructed arteries of the feet.

To the best of our knowledge, the use of bosentan in a case of SCLE-associated vasculitis inducing critical ischaemia has not been reported before. Off-label bosentan treatment was started after some frustrated therapy attempts, including two vasodilators as well as high doses of prednisolone, especially because of the critical ischaemia associated with the risk of tissue necrosis. The striking success of bosentan treatment in our patient (complete reversal of the clinical symptoms of ischaemia) was objectified by a marked improvement of repeated oscillography and a once again normal MRA.

Endothelial cells are a main site of ET production but also targets for ET (e.g. expression of pro-adhesive molecules). Vasculitis, a condition characterized by the inflammation of blood vessels, may possibly be accompanied by increased concentrations of ET. ET is known to be a potent vasoconstrictor and has several pro-inflammatory
faces [8]. Especially ET-1 enhances neutrophil chemotaxis [9] and activation, as well as the release of MMPs. ET-1 may lead to NF-κB stimulation and may subsequently stimulate the production of pro-inflammatory cytokines like IL-6, IL-8 and TNF-α [10]. The use of an oral ET dual receptor antagonist in our patient led to a rapid remission of ischaemia. This fast and sustained response had probably been achieved by potent vasodilatation. The reversal of the obstructive vasculitis documented by MRA might also at least partially be related to bosentan. The blockade of ET might have caused a down-regulation of pro-inflammatory cytokines and cells by a mechanism mentioned earlier. Corticosteroids were already terminated 4 weeks after the start of the bosentan therapy. Now, 9 months later, there is no evidence of reoccurrence of vasculitis. Bosentan might, therefore, be responsible for sustained remission. This could be interpreted as further piece of evidence of its anti-inflammatory potential in this case.

In conclusion, we think that bosentan, in this individual patient, exhibited compelling vasodilatory and anti-inflammatory effects leading to a rapid and sustained clinical improvement of the ischaemia, probably achieved by antagonization of endothelin. Bosentan might, for this reason, be regarded as therapeutic alternative in ischaemic complications caused by vasculitic syndromes resistant to standard treatment regimes.

Rheumatology key message

- Bosentan might be regarded as therapeutic alternative in ischaemic complications caused by vasculitic syndromes resistant to standard treatment regimes.

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Urinary β2-microglobulin as a sensitive marker for haemophagocytic syndrome associated with collagen vascular diseases

Sir, Haemophagocytic syndrome (HPS), phagocytosis of other blood cells by macrophages in the bone marrow, is probably induced by the activation of macrophages through inflammatory cytokines, such as IFN-γ, TNF-α, IL-1β, IL-6, IL-12 and IL-18, secreted by other cells [1]. It potentially leads to multiple organ system failure and death. It is often difficult to prove haemophagocytosis by bone marrow aspiration and the diagnosis of HPS could be delayed if pathological evidence is required prior to initiating treatment.

Serum ferritin levels have been used most frequently as a hallmark of HPS and the level of hyperferritinaemia correlates with disease activity and prognosis in adults [2]. The urine β2-microglobulin (β2m) level was reported to be a sensitive marker of HPS in children by Hibi et al. [3] in 1995. They also showed that high urinary concentrations of β2m correlate with increased levels of serum IFN-γ and high urinary β2m excretion would be the result of increased expression and shedding of cell-surface HLA class I molecules induced by IFN-γ.

We included the urine β2m level in the routine laboratory examination of all inpatients at our hospital from 2004 to 2007. Five patients were found to have HPS during their hospitalization; the estimation of urine β2m levels was extremely helpful for the diagnosis and treatment of HPS. Two typical patients are presented here.

A 39-yr-old Japanese female developed SLE in 2001 and did well until 15 May 2007, when she became febrile intermittently up to 39°C for several days. She was also found to have leukopenia and thrombocytopenia as well as liver dysfunction. The diagnosis of HPS was confirmed by examination of bone marrow aspirated from the sternum. Methylprednisolone pulse therapy (1 g for 3 days) was immediately begun followed by dexamethasone at 6 mg daily.

The urine β2m level was high at 26113 μg/g Cr initially and then increased to 124223 μg/g Cr immediately following a glucocorticoid pulse without increased blood cell counts. Since high fever continued and the level of urinary β2m increased further, the dose of dexamethasone was increased to 12 mg and CsA was added at 125 mg daily. Leukopenia and thrombocytopenia improved to some extent, and body temperature decreased slightly. However, tapering of the glucocorticoid led to recurrent fever along with an increase in the excretion of urinary β2m. Intravenous betamethasone 100 mg daily for 3 days with additional administration of mizoribine, an immunosuppressant, improved her condition and urinary β2m excretion decreased steadily thereafter (Fig. 1A).

A 44-yr-old Japanese female was diagnosed with RA in 1986. She underwent left total knee replacement in November 2006. Unfortunately, the artificial joint became infected by Enterococcus faecalis. She developed a dermal eruption on her hands, which spread to her entire trunk along with a fever of 40°C and dyspnoea 11 days after the start of teicoplanin. The white blood cell and platelet counts decreased simultaneously to 2900/μl and 17.8 × 109/μl respectively, and she was diagnosed with HPS histologically. The urine level of β2m was extremely high at 9474 μg/g Cr, which increased even further thereafter. Antibiotics were withdrawn and methylprednisolone pulse therapy was initiated at 1 g for 3 days along with parenteral CSA at 60 mg daily. The urine level of β2m decreased swiftly followed by clinical improvement (Fig. 1B).

The urine level of β2m increased sharply and remarkably before HPS began and returned to normal or near normal when