Treatment of refractory hypocomplementaemic urticarial vasculitis syndrome progressing to systemic lupus erythematosus with belimumab

Sirs,

Hypocomplementaemic urticarial vasculitis syndrome (HUVS) is a leukocytoclastic vasculitis characterised by urticarial lesions, frequently associated with fever, musculoskeletal disease and abdominal pain. Other manifestations include nephritis, uveitis, episcleritis, chronic obstructive pulmonary disease and neurological abnormalities (1, 2). HUVS cases associated with systemic lupus erythematosus (SLE) have been described, HUVS appearing prior to SLE is infrequent (3). Moderate/high doses of glucocorticoids (GC), dapsone, colchicine and hydroxychloroquine have been demonstrated as the most effective treatments for HUVS (1, 4). Immunosuppressive therapies such as methotrexate, azathioprine, cyclophosphamide and rituximab may be considered in refractory cases. Belimumab inhibits the binding of soluble B-lymphocyte stimulator (BLyS) to B-lymphocytes. It is the only monoclonal antibody approved non-renal SLE treatment (5).

We report a 55 years-old Caucasian male diagnosed with HUVS in 2005. On his first presentation, he had purpuric papules and haemorrhagic skin lesions on arms, trunk and legs, with no other clinical signs of disease in the physical examination. Hypocomplementemia C3/ C4 was observed. His medical history was inconspicuous besides being a former smoker, with no family history of rheumatic/inflammatory disease.

The initial workup of HUVS diagnosis included a skin biopsy with a histological examination, which revealed swelling of vessel walls in the papillary dermis. Direct immunofluorescence identified deposition of IgG/IgM/IgA in small vessel walls of the upper dermis; these findings were consistent with leucocytoclastic vasculitis. The manifestations were limited to the skin. HUVS was refractory to GC, fexofenadin, dapson, cyclosporine, hydroxychloroquine (HCQ), infliximab, mycophenolate-mofetil, high doses intravenous immunoglobulins and rituximab, the latter inducing a severe anaphylactic reaction. No significant improvement of the skin lesions was achieved by any of these treatments, but lesions then gradually ceased with marked hyperpigmentation.

However, several years later HUVS again worsened (Fig. 1 A-C) and new symptoms appeared. He developed polyarthritis affecting hands and elbows, as well as intermittent acrocyanosis, dyspnoea, palpitations, chest pain and fatigue. The laboratory showed elevated erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies (ANA, 1:3200), C1q antibody, leukopenia, hypocomplementaemia and proteinuria. Anti-double stranded DNA, anti-Sm, anti-Ro60/ Ro52 and antiphospholipid-antibodies as well as lupus anticoagulant were negative, D-dimer and coagulation parameters were found normal. The combination of skin lesions, arthritis, ANA, hypocomplementaemia and leukopenia enabled SLE diagnosis according to the 2019 European League against Rheumatism/American College of Rheumatology

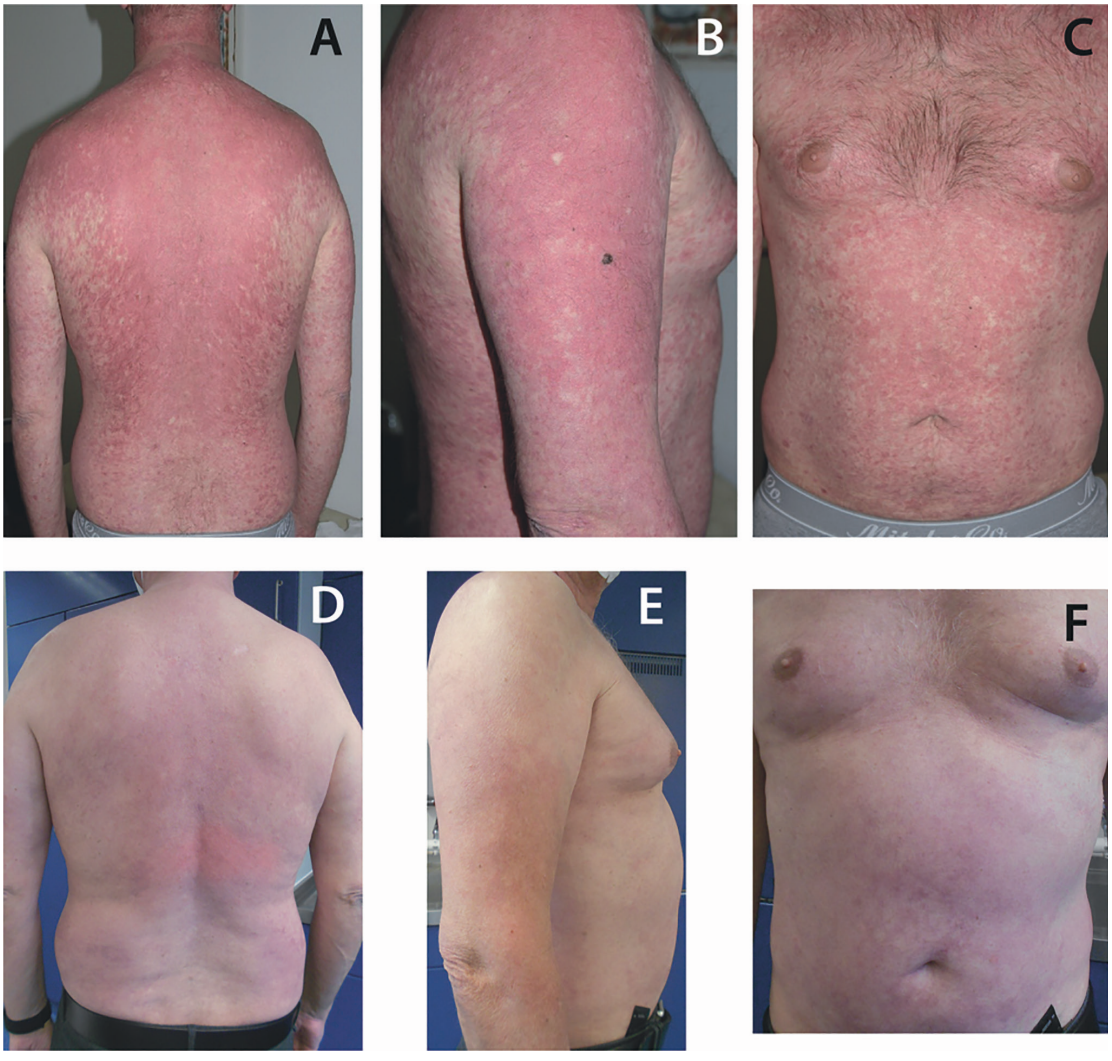

Fig. 1. **A**-**C**: HUVS skin lesions prior to commencement of belimumab treatment.
D-**F**: HUVS skin lesions after 12 weeks of belimumab.

classification criteria (6). Echocardiography showed high-grade tricuspid and mitral regurgitation and high-grade bicuspid aortic valve insufficiency explaining the dyspnoea and suggesting SLE heart involvement. Treatment with GC and HCQ (5 mg/d and 400 mg/d, respectively) was started, but the arthritis progressed toward a Jaccoud's arthropathy (JA) with manifest metacarpophalangeal and interphalangeal deformities. HUVS lesions remitted and recurred at short intervals and additionally a lupus rash developed in the face. A skin biopsy was performed and revealed a low inflammatory stage of cutaneous lupus erythematosus with areas of skin atrophy. Based on failure of GC/HCQ we started belimumab (10 mg/kg i.v./4 weeks). After 12 weeks of treatment his HUV symptoms and polyarthritis significantly improved and glucocorticoids were suspended (Fig. 1 D-F). Treatment with belimumab and HCQ was well tolerated. Heart valve reconstruction is currently being planned.

HUVS is poorly characterised. It can be associated with SLE, described in 7% to 8% of SLE patients (1, 3). Little is known about the therapy of HUVS and this case shows that it responds promptly to belimumab treatment supporting its autoimmune pathogenesis. Starting belimumab was not solely based on the worsening of HUVS but triggered by multi-organ manifestations (skin, joint, heart). HUVS with valvular heart disease and JA has been described (7, 8) and requires fast intervention. This case suggests that HUVS associated with SLE can be an indication for the start of belimumab treatment.

L. Valor-Méndez, *MD*
G. Schett, *MD*
B. Manger, *MD*

Department of Internal Medicine 3, Rheumatology and Immunology, Friedrich Alexander University Erlangen-Nuremberg and Universitätsklinikum Erlangen, Deutsches Zentrum für Immuntherapie (DZI) FAU Erlangen-Nürnberg and Universitätsklinikum Erlangen, Germany.

Please address correspondence to: Larissa Valor-Méndez, Department of Internal Medicine III, Rheumatology and Immunology, Friedrich Alexander University Erlangen-Nuremberg and Universitätsklinikum Erlangen, Deutsches Zentrum für Immuntherapie (DZI) FAU Erlangen-Nürnberg and Universitätsklinikum Erlangen, Ulmenweg 18, 91054 Erlangen, Germany. E-mail: Larissa.ValorMendez@uk-erlangen.de

Competing interests: none declared.

References

1. ALHARBI S, SANCHEZ-GUERRERO J: Successful treatment of urticarial vasculitis in a patient with systemic lupus erythematosus with rituximab. *Clin Med Insights Arthritis Musculoskelet Disord* 2020; 13: 1179544120967374.
2. MCDUFFIE FC, SAMS WM JR., MALDONADO JE, ANDREINI PH, CONN DL, SAMAYOA EA: Hypocomplementemia with cutaneous vasculitis and arthritis. Possible immune complex syndrome. *Mayo Clin Proc* 1973; 48: 340-8.
3. HER MY, SONG JY, KIM DY: Hypocomplementemic urticarial vasculitis in systemic lupus erythematosus. *J Korean Med Sci* 2009; 24: 184-6.
4. JACHIET M, FLAGEUL B, DEROUX A *et al*.: The clinical spectrum and therapeutic management of hypocomplementemic urticarial vasculitis: data from a French nationwide study of fifty-seven patients. *Arthritis Rheumatol* 2015; 67: 527-34.
5. BLAIR HA, DUGGAN ST: Belimumab: A review in systemic lupus erythematosus. *Drugs* 2018; 78: 355-66.
6. ARINGER M, COSTENBADER K, DAIKH D *et al*.: 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis* 2019; 78: 1151-9.
7. AMANO H, FURUHATA N, TAMURA N, TOKANO Y, TAKASAKI Y: Hypocomplementemic urticarial vasculitis with Jaccoud's arthropathy and valvular heart disease: case report and review of the literature. *Lupus* 2008; 17: 837-41.
8. HOUSER SL, ASKENASE PW, PALAZZO E, BLOCH KJ: Valvular heart disease in patients with hypocomplementemic urticarial vasculitis syndrome associated with Jaccoud's arthropathy. *Cardiovasc Pathol* 2002; 11: 210-6.