Löfgren syndrome as secondary autoimmune disease in a patient with B-cell depletion following rituximab treatment

Sirs,

Rituximab is increasingly used to treat several autoimmune disorders, including idiopathic nephrotic syndrome (1) and refractory cases of sarcoidosis. Sarcoidosis is a systemic granulomatous disease with a predominant involvement of T-cells. Besides, more recent research proposed an altered B-cell homeostasis in active sarcoidosis (2).

Here we present the case of a 46-year-old female patient of Caucasian descent, who presented with nephrotic syndrome in June 2007. Light and electron microscopy of a performed renal biopsy indicated minimal change disease. She was started on steroids and due to a relapsing-remitting disease course on cyclosporine A, rituximab (single dose 1g) was added in September 2014, which yielded a complete remission. Due to repopulation of B-cells a second single dose rituximab (1 g total dose) in the absence of significant proteinuria was administered in July 2015.

In October 2015, she presented with shortness of breath, bilateral ankle arthritis (Fig. 1A) erythema nodosum (Fig. 1B). A computed tomography with contrast medium revealed bilateral hilar lymphadenopathy (Fig. 1C-D). Angiotensin converting enzyme (ACE) was slightly elevated. Finally, a diagnosis of Löfgren syndrome was made after exclusion of differential diagnosis. Circulating B-cells and anti-rituximab antibodies were undetectable, while both blood and urine concentrations of rituximab were reported to be below the lower limit of quantitation. Since the patient developed two predominantly T-cell mediated autoimmune disorders, we performed an in-depth analysis of T-cell subsets including activated T-cells and found a normal distribution (Suppl. Fig. 1A 1-5). Moreover, a TCR-Vbeta repertoire analysis revealed no specific clonal pattern (Suppl. Fig. 1B-C) but an accentuated expansion of several variable beta (vb) chain segments when compared with the respective reference values. This was in line with a subsequently performed molecular T-cell clonality testing corresponding to the BIOMED-2/Euroclonality recommendations that revealed T-cell (oligo)clonality in the TCR beta locus, reflecting an exaggerated immune activation with a dominant immunospecificity (see Suppl. Fig. 2A-D).

Treatment with low dose steroids (methylprednisolone 16 mg/day) was initiated and led to resolution of the cutaneous manifestations and arthritis within days. Moreover, a repeated computed tomography scan highlighted a decrease of lymph node size (Fig. 1E-F). Steroids were gradually tapered and weaned off without recurrence of both diseases.

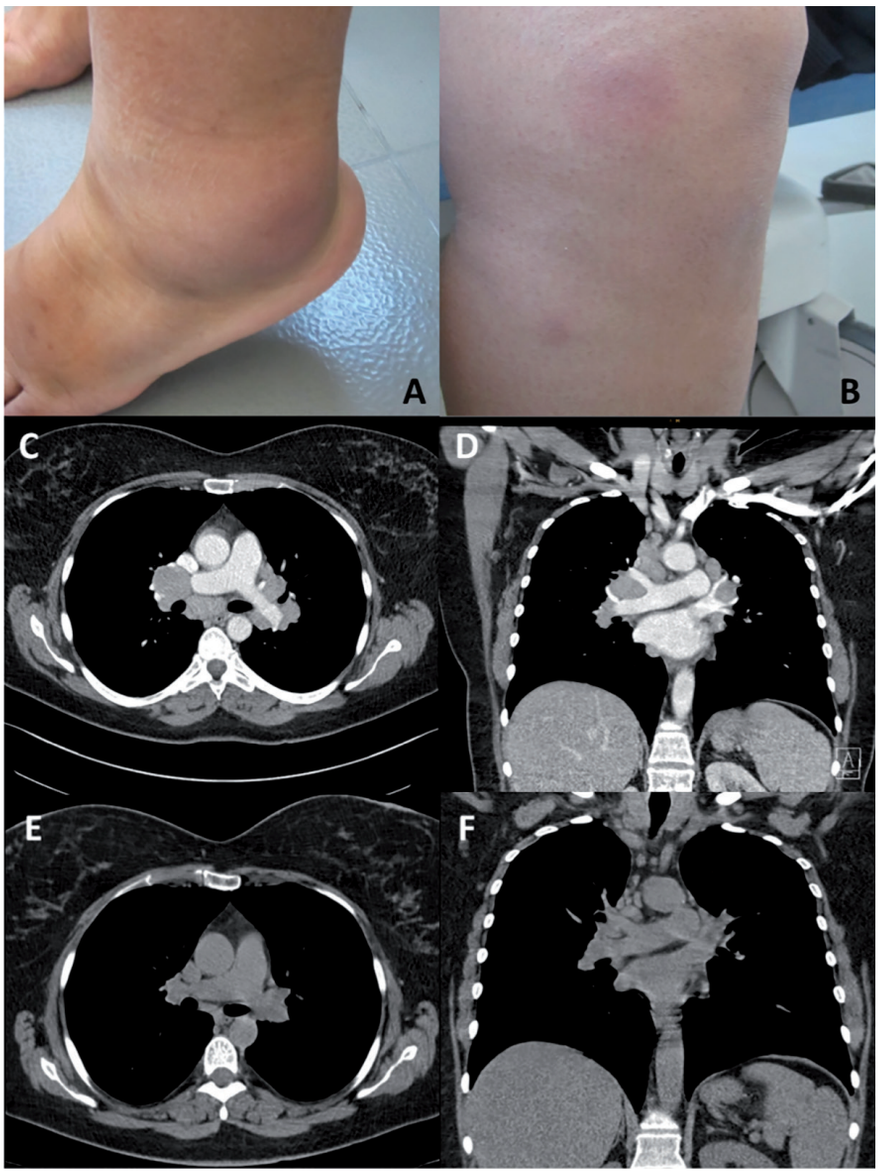

Fig. 1. Ankle arthritis (bilateral) occurred (**A**), accompanied by erythema nodosum which was restricted to both lower legs and forearm (**B**). Contrast enhanced computed tomography showed bilateral hilar lymphadenopathy in axial and coronal slices (**C** and **D**). Regression of lymphadenopathy to near-normal size in the follow-up computed tomography without contrast after initiation of treatment (**E** and **F**).

To our knowledge, this case represents the first description of a secondary autoimmune disease under complete B-cell depletion following rituximab treatment. One recent case report suggested an association between sarcoidosis onset and successful rituximab treatment in a patient with pemphigus vulgaris (3), while another found a cutaneous sarcoid-like reaction after receiving rituximab to treat microscopic polyangiitis (4). Other agents such as tocilizumab have been linked with the potential occurrence of sarcoidosis (5). In haematology, sarcoidosis-lymphoma syndrome (SLS) is a well characterised syndrome where sarcoidosis can either precede or follow a lymphoma diagnosis. A review of 39 cases found a median delay from lymphoma to sarcoidosis diagnosis of 18 months. Most patients achieved complete clinical response during follow-up (6). However, only a minority of patients received rituximab, but SLS may occur in rituximab-treated patients as well (7). As in our case, fluctuating rituximab levels despite B-cell depletion have been reported before (8) and rapid peripheral B-cell recovery due to persistent tissue-adjacent CD20+ B-cells (9) may either render the patient prone to disease relapse or onset of secondary autoimmune disorders as has been shown in this case. Despite B-cell depletion, rituximab was proposed to be specifically effective to remove autoreactive T-cells interacting with autoantigen-presenting B-cells in the immunological synapse of peripheral lymphoid organs (10), which in turn may exaggerate T-cell homeostasis and may be an explanation for a sequential autoimmune disease.

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References

1. KRONBICHLER A, BRUCHFELD A: Rituximab in adult minimal change disease and focal segmental glomerulosclerosis. *Nephron Clin Pract* 2014; 128: 277-82.
2. SAUSSINE A, TAZI A, FEUILLET S *et al*.: Active chronic sarcoidosis is characterized by increased transitional blood B cells, increased IL-10-producing regulatory B cells and high BAFF levels. *PloS One* 2012; 7: e43588.
3. GALIMBERTI F, FERNANDEZ AP: Sarcoidosis following successful treatment of pemphigus vulgaris with rituximab: a rituximab-induced reaction further supporting B-cell contribution to sarcoidosis pathogenesis? *Clin Exp Dermatol* 2016; 41: 413-6.
4. PESCITELLI L, EMMI G, TRIPO L *et al*.: Cutaneous sarcoidosis during rituximab treatment for microscopic polyangiitis: an uncommon adverse effect? *Eur J Dermatol* 2017; 27: 667-8.
5. BUSTAMENTE L, BUSCOT M, MARQUETTE CH, ROUX C: Sarcoidosis and tocilizumab: is there a link? *Clin Exp Rheumatol* 2017; 35: 716.
6. LONDON J, GRADOS A, FERME C *et al*.: Sarcoidosis occurring after lymphoma: report of 14 patients and review of the literature. *Medicine* 2014; 93: e121.
7. CHO H, YOON DH, KIM JH *et al*.: Occurrence of sarcoidosis after chemotherapy for non-Hodgkin lymphoma. *Kor J Intern Med* 2016; 31: 605-7.
8. MCDONALD V, MANNS K, MACKIE IJ, MACHIN SJ, SCULLY MA: Rituximab pharmacokinetics during the management of acute idiopathic thrombotic thrombocytopenic purpura. *J Thromb Haemost* 2010; 8: 1201-8.
9. LEANDRO MJ: B-cell subpopulations in humans and their differential susceptibility to depletion with anti-CD20 monoclonal antibodies. *Arthritis Res Ther* 2013; 15 (Suppl. 1): S3.
10. DATTA SK: Anti-CD20 antibody is an efficient therapeutic tool for the selective removal of autoreactive T cells. *Nat Clin Pract Rheumatol* 2009; 5: 80-2.