RHEUMATOLOGY ADVANCES IN PRACTICE

Letter to the Editor (Case report)

Rheumatology Advances in Practice 2021;0:1–3
doi: 10.1093/rap/rkab020
Advance Access Publication 12 March 2021

Rituximab fails to treat giant cell arteritis in a patient with ACPA-positive rheumatoid arthritis

Key message

- B cell depletion is unlikely to be of therapeutic benefit in GCA.

Dear Editor, Here we describe a patient with ACPA-positive RA who developed GCA while being treated with rituximab and MTX. The patient subsequently responded well to tocilizumab. This is the first reported case in the literature whereby GCA has been diagnosed in a patient being treated with rituximab and might guide future research into other immune therapies for GCA.

A 67-year-old woman with ACPA-positive RA was seen in clinic in October 2018 with a flare of inflammatory symptoms. She had previously been in remission after two cycles of rituximab with oral MTX 5 mg once weekly. Her symptoms were initially in keeping with a flare of RA, because there were 15 swollen and 20 tender joints. At this point, her CRP was 56 mg/l and ESR 78 mm/h, with a global visual analog scale score of 90/100. A third cycle of rituximab was organised in November 2018. By February 2019 the synovitis had improved but the CRP and ESR were persistently raised at 73 and 104, respectively, with a new normocytic anaemia (105 g/l). The inflammatory markers, along with the degree of early morning stiffness, were out of keeping with her previous rheumatoid disease. In May 2019, a patient-initiated emergency telephone clinic appointment was arranged to discuss the ongoing presence of symptoms, and the patient complained of a persistent nonspecific headache and scalp tenderness. At this point, GCA with PMR was considered and a temporal artery biopsy organised.

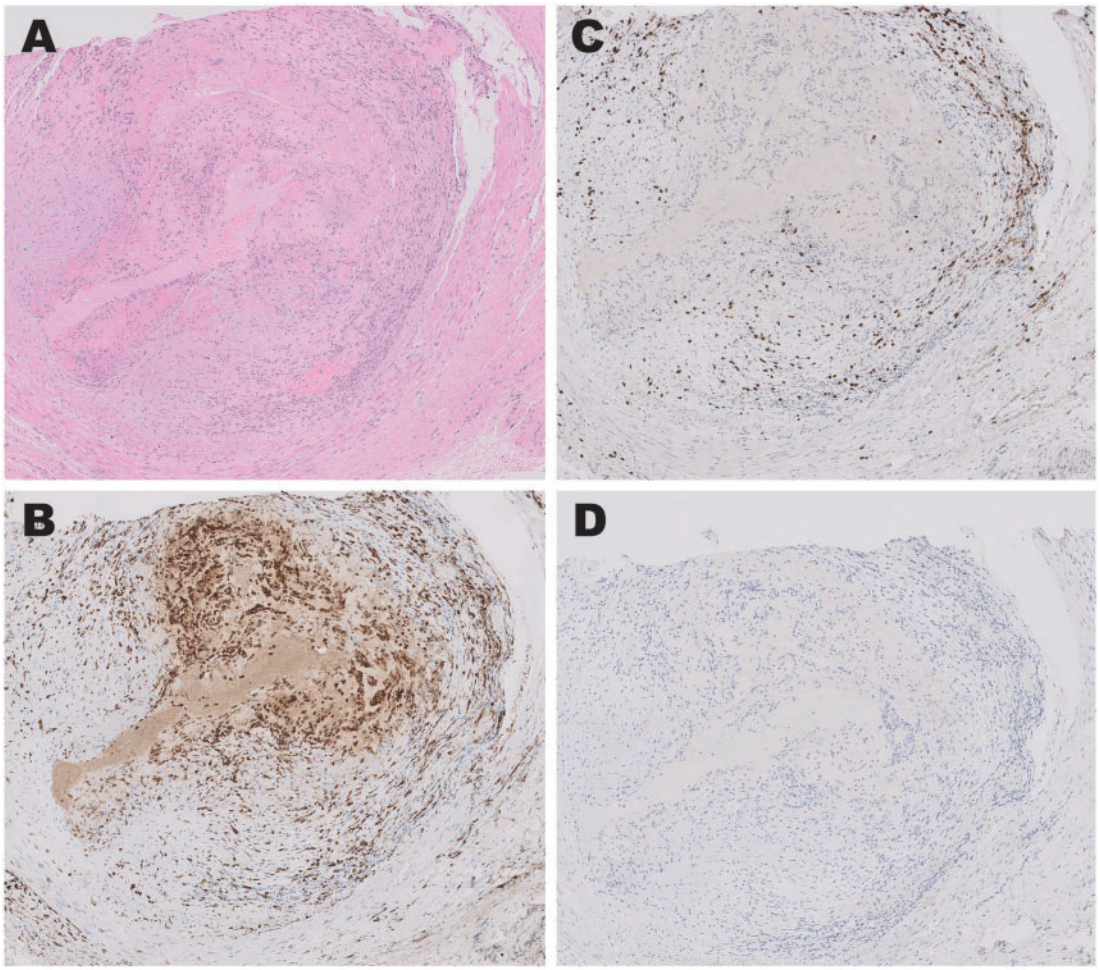
A temporal artery biopsy was performed in June 2019. The histology revealed focal areas of thickening of the tunica intima, with partial thrombosis of a medium-sized vessel, neutrophil polymorphs, lymphocytes and CD68 macrophages. The case was reviewed at a regional pathology meeting, with the consensus that the fibroblastic proliferation and lymphohistiocytic inflammatory infiltrate with resolving thrombosis were consistent with a diagnosis of GCA. Later immunostaining found that there were numerous macrophages and T cells and a paucity of B cells, B cell aggregates and plasma cells (Fig. 1). The patient's symptoms had improved somewhat with glucocorticoids (prednisolone 40 mg) started before the biopsy, which were subsequently increased to 60 mg for a full response and suppression of inflammatory markers. MTX was also increased to 7.5 mg weekly, but side effects prevented the dose from being increased any further. Given that a cycle of rituximab had been given during the onset of GCA/PMR symptoms with no improvement, the decision was made to switch biologic therapy to tocilizumab. In April 2020 her symptoms had largely resolved, and by August 2020 the patient had managed to reduce her dose of prednisolone down to 10 mg, had no tender or swollen joints, an undetectable CRP and ESR of 2 mm/h, with a rapidly resolving normocytic anaemia (haemoglobin 130 g/l).

RA and GCA are both common conditions, occurring in ~1% of the adult population > 60 years of age. Furthermore, ACPA-positive RA shares at least two known genetic susceptibility alleles with GCA: an association with an MHC class II allele, *HLA-DRB1*04* [1, 2], and a *PTPN22* polymorphism, which is known to decrease the T cell receptor activation threshold [1, 3]. It is therefore not unusual for the two autoimmune conditions to co-exist in one individual. However, in this case, rituximab was being used to control RA, which failed to stop the development of GCA/PMR. This might be suggesting that rituximab is not effective in treating vasculitis caused by GCA/PMR. There are no trials and few case reports in the literature on the topic. Rituximab has been used successfully to treat GCA, as reported by Bhatia *et al.* [4], but in the case report it was used alongside CYC, a drug known to have potent immunosuppressive actions. To our knowledge there are no other reports of rituximab and GCA in the literature.

GCA might represent an immunologically heterogeneous disease. Just as synovial biopsies in RA have discovered different pathotypes (myeloid, lymphoid and pauci-immune) that can guide the choice of biologic drug [5], there might be distinct immunophenotypes in GCA. For instance, Graver *et al.* [6] found variable numbers of T and B cells in biopsies of cranial GCA compared with extra-cranial GCA, with more extensive involvement of the descending aorta and its branches. More work is needed to ascertain whether such pathotypes exist, because it is plausible that the choice of immunomodulation might differ, leading to a personalized medicine approach to therapy. Immunophenotypes might also predict other important features of GCA, such as visual loss or progression to large vessel vasculitis, and therefore would act as useful prognostic indicators.

This case is the first reported treatment failure of rituximab for the management of GCA. However, case reports often overstate the importance of their findings, and there is an obvious inability to draw any statistical conclusions from them. That said, they represent a starting point for the design of future studies, including randomized controlled trials, and are an important building block in the advancement of scientific knowledge.

Fig. 1 Temporal artery biopsy, showing transmural inflammation and a T cell infiltrate



(**A**) Haematoxylin- and Eosin-stained cross-section of a muscular artery, showing an infiltrate of cells within the muscular wall with occlusion of the lumen. (**B**) CD45 stain (brown), showing leucocytes within the tunica intima and media. (**C**) CD3 stain (brown), confirming that the lymphocytic infiltrate consists of numerous T cells. (**D**) CD20 stain (brown), showing a paucity of B cells in the biopsy.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

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

Data availability statement

No new data were generated or analysed in support of this research.

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Accepted 23 February 2021

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