Artery tertiary lymphoid organs in giant cell arteritis are not exclusively located in the media of temporal arteries.

Graver, Jacoba Carolien; Sandovici, Maria; Diepstra, Arjan; Boots, Annemieke M H; Brouwer, Elisabeth

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With great interest, we read the article by Ciccia *et al*, about artery tertiary lymphoid organs (ATLOs) in giant cell arteritis (GCA) and the association with ectopic expression of constitutive lymphoid tissue-homing chemokines.[1] In 50 patients with biopsy-proven GCA that fulfilled the 1990 ACR classification criteria[2] and had temporal transmural inflammation, Ciccia *et al* documented the presence of ATLOs in 60% of the patients. In their study, ATLOs were defined as inflammatory aggregates that displayed a well-defined compartmentalisation of T and B cells. The authors state that ATLOs were exclusively located in the media of the temporal artery. In addition, the authors mention that the location of ATLOs in the media of the inflamed temporal artery is peculiar and deviating from the 'classic' adventitial location of ATLOs, as, for instance, seen in atherosclerosis.[3 4] However, the figures included in the article do not convincingly provide evidence that the ATLO location is in the media.

Until recently, B cells have received little attention as putative players in the immunopathology of GCA. B cells and germinal centre formation were reported to be absent from vascular infiltrates, and in spite of several attempts, no disease-specific autoantibody production has been identified.[5–7] Furthermore, lesional T cells were reported to colocalise with macrophages but not with B cells.[7] Our group was the first to report on a disturbed distribution of B cells in the peripheral blood of GCA patients. In the inflamed temporal artery, we found B cells in the adventitia but seldom in the media.[8] This finding was in line with previous reports characterising B cells in biopsy-proven GCA temporal arteries.[9,10] Thus, prior studies are in sharp contrast with the present study by Ciccia *et al*, reporting on the presence of B-cell-rich areas/ATLOs exclusively in the media. Nevertheless, the observation of Ciccia *et al* is highly interesting, as it indicates a potential role for B cells at the site of vascular inflammation in GCA.

We recently extended our previous work and stained temporal artery biopsies of 21 biopsy-proven GCA patients (71% female, mean duration of disease of 2.3±0.9 months) that fulfilled the 1990 ACR classification criteria with anti-CD20 (clone L26) and anti-CD3 (clone F7.2.38) antibodies. The median age was 73 years (range 59-89), and the erythrocyte sedimentation rate was 86 mm/hour (range 7–116). Headache was present in 17 out of 21 patients, and 18 biopsies (85%) showed transmural inflammation. At the time of biopsy, 4 out of 21 patients received glucocorticoids (GC) (duration of treatment before biopsy was 3, 11, 13 and 45 days), and three other patients received long-term GC treatment in the past but not at the time of biopsy.

B cells were present in all but one patient, and as before, most B cells were observed in the adventitia (see figure 1). Within the adventitia, B cells were located outside the lamina elastica externa which separates the adventitia and media and in proximity of the vasa vasorum. B cells were observed in varying amounts and degree of organisation ranging from a more scattered pattern to a seemingly organised pattern of B cell aggregates. Using the same definition for ATLOs as Ciccia *et al*, we found ATLOs in only 7 of 21 patients (33%). ATLOs were almost exclusively observed in the adventitia (n=7) with only one patient having ATLOs in both the adventitia and the intima. Importantly, ATLOs were not observed in the media. ATLOs were found in patients with and without GC treatment during biopsy. Of note, our analysis did not include B cell aggregates that did not fulfil the ATLO definition and/or were located in the periadventitial adipose tissue. In agreement with Ciccia *et al*, the presence of ATLOs was not correlated with the degree of inflammation, age or duration of symptoms before biopsy. In contrast to Ciccia *et al*, we did not find a correlation between the baseline inflammatory response score and the number of ATLOs. This is true for all included patients and also true for those without GC treatment during biopsy.

Our results thus confirm the presence of ATLOs in the inflamed temporal artery of patients with GCA, suggesting a role for B cells at the site of vascular inflammation. Nevertheless, in our study, ATLOs were almost exclusively located in the adventitia, which is in sharp contrast with the exclusive location of ATLOs in the media documented by Ciccia *et al*. Inflammation in GCA frequently includes adventitial fibrosis, fragmentation of the external elastic membrane and media degeneration. These changes in the vessel wall could obscure the exact location of the ATLO. In conclusion, we show that B cells in GCA organise into ATLOs and that ATLOs are mostly found in the adventitia, occasionally in the intima, but not in the media of the temporal artery. Clearly, additional studies are needed to further investigate the role of B cells in GCA pathology.

Jacoba Carolien Graver,[1] Maria Sandovici,[1] Arjan Diepstra,[2] Annemieke M H Boots,[1] Elisabeth Brouwer[1]

[1]Department of Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
[2]Department of Pathology and Medical Biology, University of Groningen, Universitair Medisch Centrum Groningen, Groningen, Netherlands

Correspondence to Dr Elisabeth Brouwer, Department of Rheumatology and Clinical Immunology, UMCG, Hanzeplein 1, 9713 GZ Groningen, Netherlands; e.brouwer@umcg.nl

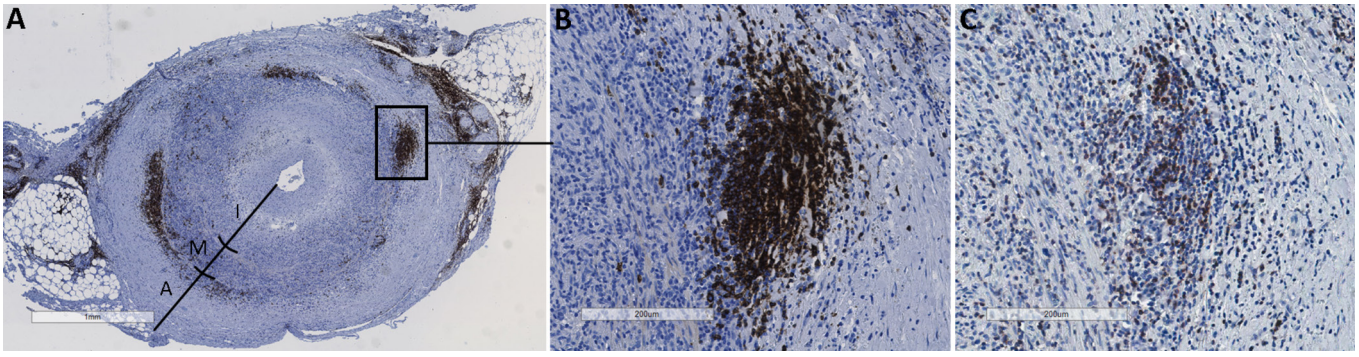

Figure 1 Artery tertiary lymphoid organ (ATLO) in adventitia of temporal artery specimen from a patient with giant cell arteritis. ATLOs were defined by organisation of inflammatory aggregates containing separate T-cell-rich and B-cell-rich areas (same definition as used by Ciccia *et al*). (A) Distribution of CD20+ B cells in the temporal artery with B-cell-rich areas in the adventitia. (B) Detailed view of ATLO in the adventitia stained for CD20+ B cells. (C) Detailed view of ATLO in the adventitia stained for CD3+ T cells. A, adventitia; I, intima; M, media.

Contributors Study design: JG, MS, AB and EB. Acquisition, analysis and interpretation of data: JG, MS, AD, AB and EB. Manuscript preparation: JG, MS, AB and EB. Overall supervision: MS, AB and EB.

Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

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