# Autoimmune Aspects of Giant Cell Arteritis

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**ABSTRACT:** Giant cell arteritis (GCA) is considered to be a T cell-dependent disease. Autoantibodies have not consistently been found in GCA. The exception is antiphospholipid antibodies (APLA), which were found in 30–80% of GCA cases. Recently, efforts have been made to seek autoantibodies in GCA using newer methods of detection: serological identification of antigens by recombinant cDNA expression cloning, and a proteomic approach. In these studies, lamin C (a nuclear envelope antigen) was recognized by antibodies in 32% of GCA sera and none of the controls. Other autoantigenic proteins were also identified: lamin A, vinculin (a cytoskeleton antigen), and annexin 5 (an endothelial protein). In a recent study, 92% of 36 patients with GCA and/or polymyalgia rheumatica (PMR) had autoantibodies to a human ferritin peptide (the heavy chain N-terminal); 89% had antibodies to bacterial ferritin peptide of *Staphylococcus epidermidis*. The significance of these findings needs to be studied further. GCA may be a part of the newly described ASIA syndrome (autoimmune syndrome induced by adjuvants). A recent study from Italy reported 10 cases of GCA/PMR within 3 months of influenza vaccination. These comprised 50% of all cases of GCA/PMR diagnosed during the 6 year period of the study. Another 11 cases of GCA following influenza vaccinations were reported. GCA pathogenesis involves all branches of the immune system, including antigen-presenting cells, T cells and B cells, and autoantibody formation is not uncommon. GCA etiology remains unknown, but may be associated with exposure to bacterial or viral antigens.

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**KEY WORDS:** giant cell arteritis (GCA), polymyalgia rheumatica (PMR), autoantibodies, ferritin, autoimmune syndrome induced by adjuvants (ASIA), antiphospholipid antibodies

Seasonal fluctuations and cyclic patterns have been observed in the incidence of giant cell arteritis, suggesting an environmental, possibly infectious, etiology of the disease. However, no clear association of GCA with any organism has been identified. The pathogenesis of GCA has been extensively studied, but it is still not fully understood. It is considered to be a T cell-dependent disease [1]. Upon dendritic cell activation in the adventitia by an unknown antigen (or antigens), CD4 T cells are recruited and polarized into Th1 and Th17 lines, producing interferon-gamma and interleukin-17, respectively, as their main cytokines. The resulting production of cytokines and activation of macrophages and vascular smooth muscle cells induce systemic manifestations, vascular remodeling and local ischemic manifestations [2-4]. Macrophages, often forming giant cells, are the major source of a variety of cytokines in arteritic lesions, such as IL-1β, IL-6, tumor necrosis factor-alpha, transforming growth factor-beta, other growth factors such as platelet-derived growth factor, and metalloproteinases. MMPs are implicated in the destruction of the internal elastic lamina, facilitating migration of myofibroblasts towards the intima, which together with the effects of platelet-derived growth factor, eventually result in intimal hyperplasia and luminal obstruction.

**The pathogenesis of giant cell arteritis involves all branches of the immune system, including antigen-presenting cells, T cells and B cells/plasma cells, and autoantibody formation is not uncommon**

## AUTOANTIBODIES IN GCA

Autoantibodies were not consistently found in GCA, although plasma cells were found in the adventitia in 7–24% of temporal artery biopsies from patients with GCA [5]. The exception was antiphospholipid antibodies, which were found in 30–80% of GCA cases [6-9]. Other related autoantibodies, such as anti-beta2 glycoprotein 1 were found in 10% of the cases [9]. However, most studies did not find significant correlations between the presence of antiphospholipid antibodies and ischemic complications in GCA patients [7-9].

Recently, efforts have been made to look for autoantibodies in GCA using new methods of detection, such as the proteomic approach and serological identification of antigens by recombinant cDNA expression cloning. In one study the cDNA library (100,000 clones) was screened for antigens reacting with immunoglobulin G antibodies in GCA sera [10]; 33 antigens were positive but most of them reacted also with normal control sera. Lamin C (a nuclear envelope antigen) was recognized by antibodies in 32% of GCA sera but none of the healthy controls. However, anti-lamin antibodies are not disease-specific and have been previously described in systemic lupus erythematosus, autoimmune liver diseases, antiphospholipid syndrome and other autoimmune conditions [11].

GCA = giant cell arteritis

IL = interleukin
MMPs = metalloproteinases

In another study, using the proteomic approach, 30 endothelial cell antigens and 19 vascular smooth muscle cell antigens were recognized by most GCA sera but not by healthy controls [12]. Some of these proteins included lamins A and C, vinculin (a cytoskeleton antigen), annexin A2 and A5 (endothelial antigens), and several mitochondrial antigens. Most of the identified antigens interacted with growth factor receptor-bound protein 2, a protein involved in vascular smooth muscle cell proliferation.

In a recent study, 92% of 36 patients with GCA and/or polymyalgia rheumatica had autoantibodies to a human ferritin peptide (the heavy chain N-terminal) [13]. In addition, 89% had antibodies to bacterial ferritin peptide of *Staphylococcus epidermidis*. Anti-ferritin antibodies were found in much lower rates in disease controls – SLE (29%), lymphoma (6%), rheumatoid arthritis (2%) – and in healthy blood donors (1%). A subsequent study reported that combining three human ferritin peptides as antigens further increased the sensitivity of the test without affecting specificity [14]. Following these reports, another group of researchers reported their experience with anti-ferritin antibodies in GCA [15]. They found a test sensitivity of 82% for this autoantibody in biopsy-positive GCA patients prior to corticosteroid treatment. Anti-ferritin antibodies were found in 34% of disease controls (patients with diseases other than GCA) and in 3% of healthy controls. The etiological, pathogenetic and clinical significance of these findings need to be studied further.

**Most patients with GCA have autoantibodies to human and bacterial ferritin peptides; this observation may advance the diagnostic capabilities for this condition**

#### GCA AND ASIA SYNDROME

GCA may be a part of the newly described ASIA syndrome (autoimmune syndrome induced by adjuvants) [16]. A recent study from Rome, Italy, reported 10 cases of GCA/PMR occurring within 3 months of influenza vaccination [17]. These cases comprised 50% of all cases of GCA/PMR that were diagnosed during the 6 year period of the study. All were females. One patient had a relapse 2 years later following influenza revaccination. Eleven additional cases of GCA following influenza vaccinations have been reported [17]. In addition, several studies showed seasonal variations in GCA onset, suggesting environmental effects [18-20].

**GCA etiology remains unknown but could be associated with exposure to bacterial or viral antigens following infections or vaccinations**

In conclusion, GCA pathogenesis involves all branches of the immune system, including antigen-presenting cells, T cells and B cells/plasma cells, and autoantibody formation is not uncommon. The cause of GCA remains unknown, but it may be related to exposure to bacterial or viral antigens.

SLE = systemic lupus erythematosus
PMR = polymyalgia rheumatica

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