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Major review

New developments in giant cell arteritis

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ABSTRACT

Giant cell arteritis (GCA) is a medium-to-large vessel vasculitis with potentially sight- and life- threatening complications. Our understanding of the pathogenesis, diagnosis, and treatment of GCA has advanced rapidly in recent times. The validity of using the American College of Rheumatology guidelines for diagnosis of GCA in a clinical setting has been robustly challenged. Erythrocyte sedimentation rate, an important marker of inflammation, is lowered by the use of statins and nonsteroidal anti-inflammatory drugs. Conversely, it may be falsely elevated with a low hematocrit. Despite the emergence of new diagnostic modalities, temporal artery biopsy remains the gold standard. Evidence suggests that shorter biopsy lengths and biopsies done weeks to months after initiation of steroid therapy are still useful. New imaging techniques such as positron emission tomography have shown that vascular inflammation in GCA is more widespread than originally thought. GCA, Takayasu arteritis, and polymyalgia rheumatica are no longer thought to exist as distinct entities and are more likely parts of a spectrum of disease. A range of immunosuppressive drugs have been used in conjunction with corticosteroids to treat GCA. In particular, interleukin-6 inhibitors are showing promise as a therapy.

1. Introduction

Our understanding of the pathogenesis, taxonomy, diagnosis, and therapy of giant cell arteritis (GCA) has continued to evolve over the past decade. New diagnostic tools are available, and therapies besides the traditional use of corticosteroids are being reported. We do not intend to provide a comprehensive review but will evaluate the role of these new developments in the diagnosis and treatment of GCA.

2. Classical taxonomy

In 1990, the American College of Rheumatology (ACR) developed diagnostic classification criteria for GCA.[85] They compared 214 patients with a clinical diagnosis of GCA made by a rheumatologist to 593 patients with other vasculitides (including Churg-Strauss Syndrome, granulomatosis with polyangiitis, hypersensitivity vasculitis, Henoch–Schönlein purpura, Takayasu arteritis, polyarteritis nodosa, arteritis

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associated with a myeloproliferative disorder, and lymphomatoid granulomatosis). Thirty-three clinical variables were chosen to attempt to discriminate between patients with clinically diagnosed GCA patients and those with these other vasculitides. It was concluded that if a patient met 3 of the following 5 criteria, a diagnosis of GCA could be made: 1) age 50 years or older, 2) new-onset localized headache, 3) temporal artery tenderness or decreased temporal artery pulse, 4) erythrocyte sedimentation rate (ESR) of at least 50 mm/hour, and 5) abnormal artery biopsy specimen characterized by mononuclear infiltration or granulomatous inflammation.

The use of the ACR criteria for the clinical diagnosis of GCA has recently been robustly challenged. Murchison and colleagues compared the ACR diagnostic criteria to temporal artery biopsy results in a group of patients from one ophthalmological clinic.[123] One-fourth of the patients with positive temporal artery biopsies would not have met sufficient clinical ACR criteria for the correct diagnosis and might have suffered severe visual consequences without histological confirmation and treatment. Part of the explanation for this is that approximately 20% of patients with GCA present with only "occult" GCA.[159] Furthermore, Murchison and colleagues found that 28.3% met the ACR clinical criteria, but had a negative temporal artery biopsy. All the patients who had a negative temporal artery biopsy had their corticosteroid treatment ceased immediately without suffering visual complications; thus, 10% of the total cohort was spared inappropriate exposure to this potentially debilitating treatment. In this group, the negative pathology prevented the potential complications of long-term corticosteroid treatment. In a study of patients treated with corticosteroids for GCA, 58% developed at least one major steroid-related complication when followed for an average of 3 years.[125]

There are several reasons why the ACR criteria have limited value in a clinical setting. First, the criteria were developed simultaneously with criteria for other vasculitides such as polyarteritis nodosa and granulomatosis with polyangiitis. They were not established to differentiate patients who have vasculitis from those who do not have vasculitis for diagnostic purposes, but rather to distinguish a specific type of vasculitis among patients with various vasculitides. In this context, the ACR criteria have a reported sensitivity of 93.5% and a reported specificity of 91.2% for the classification of GCA compared with other vasculitides.[85] The criteria, however, do not have the same positive and negative predictive values in patients who may not have a previously established diagnosis of vasculitis because the capacity of any set of diagnostic criteria to identify a patient with GCA is better when disease prevalence is high, as in rheumatology clinics, rather than when disease prevalence is low, such as ophthalmology or general medical clinics. Furthermore, if the criteria are applied to a population in which the prevalence of GCA is low, the false positive rate will also be high.[141]

There are also limitations originating from how the ACR criteria were established. Their validation was through multicenter data and retrospective diagnosis with the "gold standard" being the diagnosis of the referring rheumatologist.[141] Histological confirmation was not required. In fact, the data set included some patients classified as GCA who never had a biopsy or who had a negative biopsy result. Hence, presently GCA can best be diagnosed by histopathologic examination of a temporal artery biopsy. The diagnosis of biopsy-negative GCA should be made with caution after extensive review of the pathology and clinical information.[38]

3. Immunopathology

Our understanding of the immune mechanisms involved in GCA has advanced.[175] Distinct immune processes have been implicated in the early and late phases of the disease.

3.1. *Vascular dendritic cells*

GCA begins with the activation of vascular dendritic cells that are embedded in the vessel walls. These cells monitor the tissue environment for danger signals including infectious agents, products of tissue breakdown, metabolic abnormalities, and deposition of irritating agents.[175]

Weyand and colleagues have shown that dendritic cells are crucial to the pathogenesis of GCA.[101] In a mouse model of GCA, whereby human arteries with biopsy confirmed GCA are engrafted on to immune compromised mice, depletion of vascular dendritic cells (by use of antidendritic cell antibodies) protected them from inflammatory attack.[111] They have also shown that dendritic cells acquire a fully developed phenotype of highly activated dendritic cells while in the arterial walls, rather than migrating to lymph nodes where dendritic cells normally become activated, a phenomenon described as "trapping." When normal medium-sized arteries were engrafted into the same GCA mouse model, the resident population of immature dendritic cells was unable to stimulate T cells; however, in arteries from patients with polymyalgia rheumatica (PMR) dendritic cells were mature, and hence able to release chemokines CCL19 and CCL21 as well as attract, retain, and activate T cells that originated from GCA lesions.[111]

Vascular dendritic cells have also been implicated in defining the tissue tropism of GCA. The expression profile of toll-like receptors, typically expressed by dendritic cells, was found to be different in 6 different vascular territories (temporal, carotid, subclavian, aorta, mesenteric, and iliac).[135] This has led to the theory that these different vascular territories specialize in surveillance for specific pathogens. Hence, they are also susceptible to vessel specific immune abnormalities. Furthermore, vascular dendritic cells determine the morphology of the inflammatory response. Although typically temporal artery specimens in GCA demonstrate panarteritis, in a subset of cases, the inflammatory infiltrate can be arranged around the vasa vasorum in the adventitia—a periarteritis. In experimental models of GCA, toll-like receptors 4 ligands consistently cause panarteritis, whereas periarteritis emerges after stimulating vascular dendritic cells with toll-like receptors 5 ligands.[44]

3.2. *T-cell–mediated effects*

The immunopathology of GCA shows a distinction between the early and late stages of the disease. In patients who underwent multiple temporal artery biopsies both early in