

OCCURRENCE OF GIANT CELL ARTERITIS...SUDDENLY

BY **Brian R. Younge MD,*** Cornelia M. Weyand MD PhD, AND Jorg J. Goronzy MD PhD

ABSTRACT

Purpose: To define the kinetics and mechanisms of frank arteritis onset in patients with giant cell arteritis.

Methods: Cytokines were analyzed from tissue of a patient before and after the development of arteritis.

Results: A temporal artery biopsy specimen from a patient with giant cell arteritis showed no pathologic changes on microscopic examination, but there was evidence of early tissue activation of inflammatory markers. A specimen from the contralateral artery 12 days later had high levels of IL-18 transcripts and abundant transcripts for CCL19. Also, CD83 and IL-1 were present, confirming that the vascular dendritic cells had fully matured. This second biopsy specimen showed floridly positive giant cell arteritis on histopathologic examination.

Conclusions: Partial activation of vascular dendritic cells is typically seen in patients with polymyalgia rheumatica in whom no inflammatory infiltrates are seen on histomorphologic examination. Dendritic cells become activated at an early stage of arteritis, beginning the pathologically evident arteritis, and are fully matured in microscopically florid arteritis.

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INTRODUCTION

Polymyalgia rheumatica and giant cell arteritis may occur as variations of the same disease along a continuum, with different manifestations depending on the factors or events that activate dendritic cells. There are racial predilections, a sex difference, and a high incidence related to older age. Temporal artery biopsy, still the criterion standard of diagnosis for giant cell arteritis, may show no evidence of arteritis at one extreme and florid arteritis at the other. The timing of the biopsy is important because the time between negative and positive findings may be as short as a few days. A biopsy within that period may be the reason for *skip areas*, in which minimal microscopic evidence is present and present in only some areas of the vessel.

METHODS

Institutional review board approval was obtained for these studies, and approval concerning care of animals for the animal studies was obtained. For several years while doing temporal artery biopsies at Mayo Clinic, we have studied tissue samples of the artery placed under the skin of T-cell and B-cell-deficient mice, also called severe combined immunodeficiency (SCID) mice. This tissue survives indefinitely in the mouse, with all the pathologic and cytokine reactions preserved.¹ The mouse supplies the nutrition and oxygen, and the arteritis continues uninterrupted. Studies of this model have been described in numerous publications relating to the cytokines and tissue-activating factors.² Tissue cytokines/chemokines and the dendritic cell activation marker CD83 were quantified by real-time polymerase chain reaction with appropriate primer sets.

CASE PRESENTATION

A 74-year-old Caucasian man presented with polymyalgia rheumatica and new-onset headaches. He stated that he had been "just feeling terrible" for 6 to 8 weeks. At presentation, his erythrocyte sedimentation rate (ESR) was 65 mm/h and the C-reactive protein level was 5.2 mg/dL. His physicians suspected that he had temporal arteritis, and a biopsy specimen was taken from 1 side. Biopsy results were clearly negative on both frozen section and final pathologic review (Figure 1). He was not treated initially.

When he returned 12 days later, his polymyalgia rheumatica was much worse, and he had a bad headache, scalp tenderness, and jaw claudication. The ESR was 100 mm/h, and the C-reactive protein level had doubled. A biopsy specimen from the contralateral temporal artery was floridly positive (Figure 2).

RESULTS

To study the 2 specimens further, a part of each specimen was analyzed for tissue cytokines and chemokines and for CD83 transcription by quantitative polymerase chain reaction. The artery specimen from the initial biopsy expressed no CD83 or IL-1, low levels of IL-18, and high levels of the chemokine CCL19. This specimen appeared to be pathologically normal and looked like the artery from a patient with polymyalgia rheumatica. It is known that there is partial activation of dendritic cells and sometimes a low-grade activation of T cells without any apparent pathologic changes (Figure 1). The specimen from the second biopsy, collected 12 days after the first, expressed CD83, IL-1, high levels of IL-18, and very high levels of CCL19. Pathologically, it looked typical of giant cell arteritis (Figure 2).

From the Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota. Dr Weyand and Dr Goronzy are now with the Lowance Center for Human Immunology, Emory University School of Medicine, Atlanta, Georgia.

*AOS presenter.

Bold type indicates AOS member.

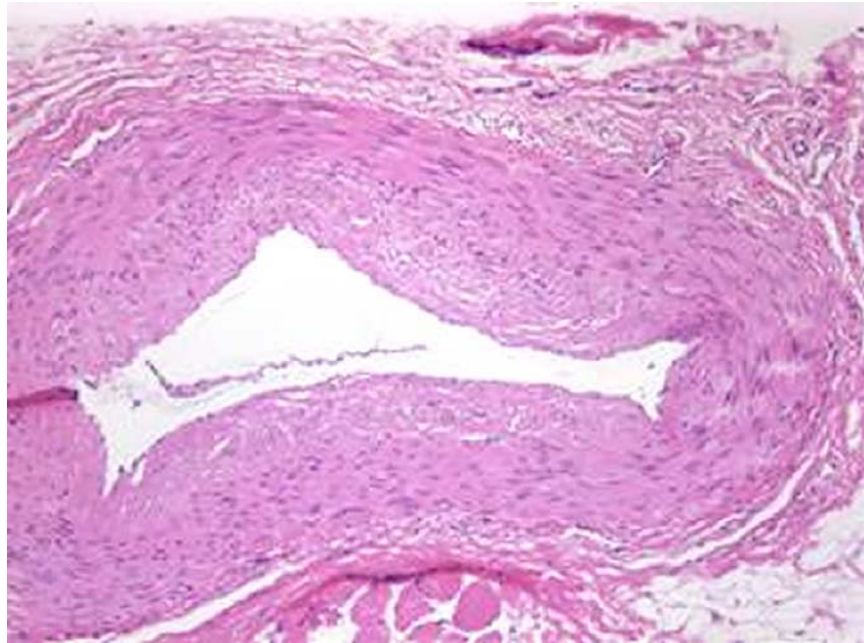


FIGURE 1

Normal appearance of temporal artery. There are no signs of an inflammatory response, and the intima and elastica are intact (hematoxylin-eosin, $\times 40$).

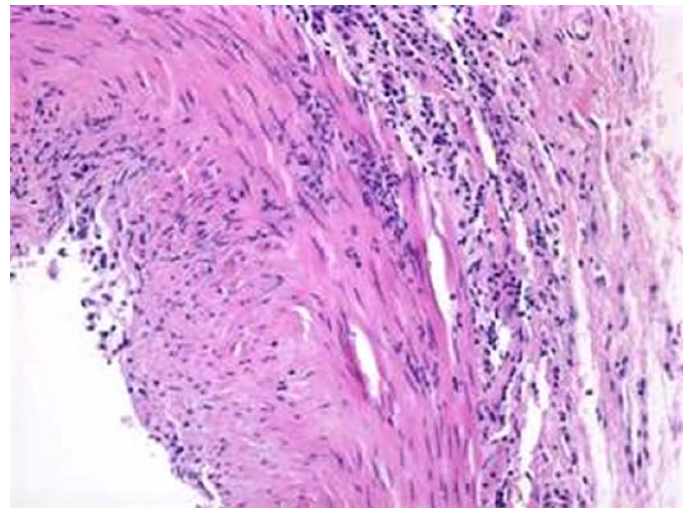
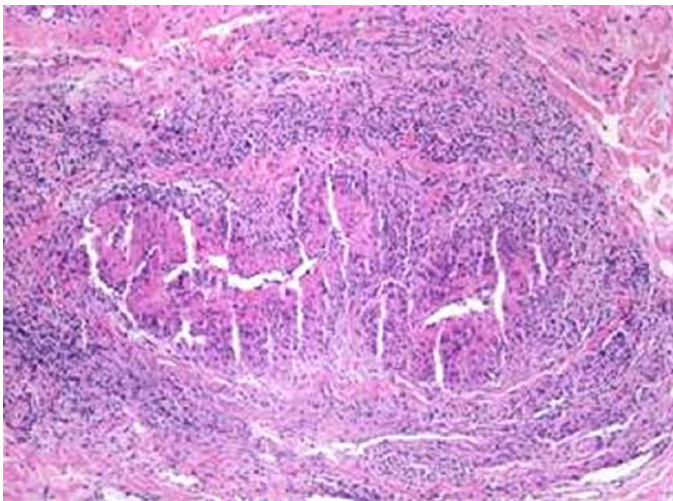


FIGURE 2

Marked inflammatory response in temporal artery (contralateral to artery shown in Figure 1 and 12 days later). Left, Many lymphocytes are present, the lumen is narrowed, and inflammatory cells are in all tissue layers of the specimen (hematoxylin-eosin, $\times 100$). Right, Higher magnification shows the predominantly lymphocytic infiltration of all layers of the vessel and an occasional giant cell (hematoxylin-eosin, $\times 200$).

DISCUSSION

Within only 12 days, the pathologic appearance of the biopsy specimens changed dramatically from definitely negative to floridly positive, with infiltrating lymphocytes, polymorphonuclear cells, early giant cells, elastic lamina fragmentation, and a grossly narrowed lumen. The presence of IL-18 and CCL19 at the initial biopsy suggests that the pathologic changes were imminent, but there was as yet little IL-18 and no CD83 or IL-1. Thus, dendritic cells had not been fully activated, and no pathologic changes were seen on histologic sections. Clinical testing suggested that there was a considerable inflammatory response initially, and the erythrocyte sedimentation rate and C-reactive protein levels essentially doubled by the time of the second biopsy. Analysis of the cytokines from the second biopsy 12 days later showed marked elevation of all the markers of inflammation and dendritic cell maturation.

Much has been written about the correlation of clinical symptoms and laboratory values with biopsy results, and Younge and colleagues³ have created a somewhat cumbersome formula that uses logistic regression and multivariate analysis of the probability of a positive temporal artery biopsy. Clinical judgment is still the most important factor in deciding whether and when to do a temporal artery biopsy.

Given the observations on the case reported here, one might speculate about the usefulness of performing bilateral simultaneous biopsies on every patient suspected of having giant cell arteritis. The hope would be to increase the yield of positive specimens instead of waiting days or weeks before sampling the contralateral side. The concordance is quite high between the 2 sides—both sides are either negative or positive, with a few exceptions—and one never sees negative biopsy results from 1 side and floridly positive results from the other when the biopsy samples were taken the same day. There may be an inconspicuous inflammatory response in a few areas of a vessel on only 1 side. This subtle finding probably reflects the early activation of the inflammatory process, which has been reported in 2% to 3% of cases.³ Warrington and colleagues indicated a positive biopsy finding on the contralateral side in 7% of patients who had biopsy samples taken from both sides on the same day, but that finding was from more recent patients at Mayo Clinic and was retrospective in nature (American College of Rheumatology Annual Meeting, 2005. Poster).

The timing of the biopsy may also account for patients having a negative biopsy result from a referring physician, only to have clearly positive results a few weeks later at another institution. Furthermore, a chance timing of the initial biopsy at the onset of the earliest inflammatory response, when pathologically discernible changes first appear, may well explain the skip areas in vessels that are pathologically negative in 1 area yet positive in another. Our pathologists have never seen a negative area in 1 part of a vessel with floridly positive areas elsewhere in the same specimen.

The mouse model provides considerable insight in terms of cytokine responses and the response to corticosteroids. Corticosteroids given to the mouse in doses equivalent to doses of 60 to 80 mg of prednisone in humans produce a dramatic decrease in cytokine tissue levels but a slow resolution of the pathologic response. Large dosages, equivalent to 1 g/day of intravenous corticosteroids, produce a rapid resolution of the pathologic changes. A recent clinical trial of megadose corticosteroids vs standard oral corticosteroids in humans showed an accelerated response in the megadose group.⁴

The duration of treatment in humans varies and is modified by clinical and laboratory responses; with a slow taper from large doses of prednisone, giant cell arteritis appears to take about a year to resolve. My colleagues and I are studying second biopsies from patients who had positive biopsy findings initially. We are studying groups of 10 patients each at intervals of 3, 6, 9, and 12 months after the initial biopsy. Preliminary results correlate fairly well with the clinical observation that 9 to 12 months pass before resolution occurs. Thus, after it is established, the pathologic response takes many months to resolve. Starting corticosteroid therapy before a biopsy will not immediately reverse the pathologic changes, even though the inflammatory response is dramatically reduced within a few hours. Whether the pathologic response can be reversed at the inception of the inflammatory response, before full activation of dendritic cells, is unknown.

CONCLUSIONS

We have provided clinical and experimental evidence that dendritic cells may be partially activated and cytokine levels partially increased in patients with polymyalgia rheumatica before the development of frank arteritis. Temporal artery biopsy findings may not be positive at this stage. The transition to active arteritis probably occurs very quickly, within a few days, and is accompanied by greatly increased levels of cytokines and the maturation of dendritic cells with the histopathologic response characteristic of giant cell arteritis. Exactly what triggers this change is unknown. Further clinical studies coupled with laboratory research are likely to answer this in the near future.

ACKNOWLEDGMENTS

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PEER DISCUSSION

DR ROBERT C. SERGOTT: The authors have provided a detailed, instructive, and invaluable case presentation that merges precise clinical observations with elegant immunologic investigations. This study illustrates the ideal of translational research. Here are the four points for immediate translation to our clinical care of patients:

1. Although polymyalgia rheumatica and giant cell arteritis were originally described as separate entities, they are truly interrelated entities both clinically and immunologically.
2. The immunologic transition of vascular dendritic cells from immature to mature cells is pivotal to the clinical conversion of polymyalgia rheumatica to giant cell arteritis. Detection of this process is critical to identify those patients at risk for visual loss.
3. In Philadelphia, we have never advocated simultaneous temporal artery biopsies, reserving that procedure only for cases persistently suggestive of giant cell arteritis despite a first negative biopsy. The authors now have provided strong immunologic support to advocate only unilateral biopsies. They have demonstrated that giant cell arteritis can clearly transition from negative to positive histopathology in a matter of days. Harvesting two negative simultaneous biopsies eliminates the possibility of a second biopsy when the disease process may have advanced to the level of fulminant arteritis.
4. The severe combined immunodeficiency mouse model [SCID] has unequivocally provided insight into the cytokine and cellular processes of the polymyalgia rheumatica to giant cell arteritis conversion. Moreover, this model strongly supports initial treatment of all patients with giant cell arteritis with high-dose, intravenous pulse methylprednisolone therapy rather than oral prednisone.

Do these findings relate to thrombocytosis? First described in 1963, thrombocytosis in giant cell arteritis has been discussed briefly at various intervals in the peer-reviewed literature.¹⁻⁶ More recently, measurement of the platelet count has been recommended to enhance the laboratory diagnosis of giant cell arteritis in conjunction with erythrocyte sedimentation rates and C-reactive protein levels.⁶

Whether this elevation in the platelet count is a truly important pathogenetic change or whether it is merely an interesting epiphenomenon remains unknown. However, since the visual morbidity of giant cell arteritis is directly related to a vaso-occlusive arteritis, it is tempting to speculate that this thrombocytosis (which is not present in polymyalgia rheumatica) may have some pathogenetic significance in the obstruction of the ophthalmic circulation. I would like to ask the authors if any of their clinical and experimental work has examined the thrombocytosis question. Because the initial observations of thrombocytosis in giant cell arteritis all were reported from Scandinavia, the observations of the Mayo Clinic in Rochester, Minnesota, where there is a large Scandinavian population, may have important immunopathogenetic significance.

In summary, the present paper represents an innovative and important contribution to the understanding of giant cell arteritis, one of the most devastating diseases in ophthalmology. The paper is the latest highly noteworthy addition to the proud lineage of the Mayo Clinic in unravelling the mysteries of giant cell arteritis. Dating back to the 1950s according to a review by Dr Younge and myself, physicians and surgeons from the Mayo Clinic have authored 88 papers about giant cell arteritis, a truly remarkable accomplishment.

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DR. MALCOLM L. MAZOW: When I was senior medical student, I saw a patient with giant cell arteritis involving the arteries that supply blood to the abdomen. I am curious to learn, in view of all the work that has been done on this subject at the Mayo Clinic, if

there is any correlation between the giant cell arteritis that we as ophthalmologists see and the giant cell arteritis with abdominal or gastrointestinal involvement.

DR. RALPH C. EAGLE, JR.: No conflicts. One thing you did not mention was the length of the original biopsy. It has been stated that an adequate temporal artery biopsy should be 2 cm in length. Another important factor is the number of transverse sections that are submitted for pathologic evaluation. I have seen biopsies with skip lesions where the arteritis involves only one or two of ten transverse sections. I have also seen cases with involvement of smaller supplementary arterioles without inflammation of the main artery. Was the original biopsy adequate?

DR. ALLAN J. FLACH: No conflict. You sure showed us how wonderfully visible black on white slides are for making presentations. Thank you for that. If you had a patient with symptoms highly suggestive of giant cell arteritis with superficial temporal artery involvement and you had performed a biopsy on one side that was negative, would you biopsy the other side to verify a pathologic diagnosis to support your decision to begin possibly toxic corticosteroid therapy?

DR. BRUCE E. SPIVEY: Searching for a conflict. The comment by Dr. Sergott that giant cell arteritis is a major cause of malpractice for ophthalmologist is not borne out by data from OMIC, the Ophthalmic Mutual Insurance Company. Brain tumors are a major cause of ophthalmic malpractice suits, but patients with giant cell arteritis are not. This is just a comment.

DR. BRIAN R. YOUNGE: I would like to thank Dr. Sergott very much for his remarks. He is very kind and this is a very controversial area in neuro-ophthalmology. He and I happen to agree on some of the things that we have discussed together. The migration of the dendritic cells from inactive to active is probably also being seen in other areas. We heard this discussed on the first day and also in the papers on macular disease. The dendritic cells are probably very active in tissues throughout the body and the mouse studies certainly are useful for studying this kind of response. Thrombocytosis probably occurs. In many patients with positive biopsies, the platelet count is considerably elevated and the occlusion of the vessels is probably due in part to the thickening of the wall, narrowing of the lumen, and some thrombosis that occurs within the vessels. If this occurs in the ophthalmic artery system you will likely have big troubles with visual loss. Sometimes it is like a snowball going down the hill that keeps gathering snow and there is nothing you can do to stop the process from occluding the vessel. We have all treated patients with systemic corticosteroids after one eye has become blind and observed the same clinical course in the other eye despite treatment. Giant cell arteritis certainly occurs elsewhere in the body and occasionally we are asked to perform a biopsy in a patient who has been studied for peripheral vascular disease and whose arteries appear very peculiar angiographically. Sometimes after aortic valve replacement histological changes of giant cell arteritis are found in the tissue in the recipient valve and frequently the temporal artery biopsy will be positive in these patients. I try to obtain a specimen of superficial temporal artery that is at least 2 cm in length from one side only. Although it is somewhat technically difficult to perform, a 2 cm biopsy is a reasonable amount of tissue to take. The neurosurgeons are used to slashing open the scalp and taking 5 or 6 cm section of artery. Ophthalmologists who are accustomed to using cotton tipped applicators just do not like to do this. Arterial tissue 2 cm long is usually sufficient to make the diagnosis. I advise ophthalmologists not to perform a biopsy on the other side, even if they are suspicious of the arteritis. If the symptoms change for the worse in the near future, then they will still have something to biopsy. If the physician still decides to treat the patient with corticosteroids, then they usually do so with lesser doses than they would for someone with symptoms of polymyalgia rheumatica. If the symptoms progress or do not improve as quickly as expected, then the physician may subject them to another biopsy or refer them for biopsy. I believe that is an important to have a second specimen available for biopsy in the future. I appreciate the comments. Thank you very much.