Supplement to

Practical Neurology®

RT Retina Today

May 2018

DIAGNOSING AND TREATING GIANT CELL ARTERITIS

WITH VISUAL AND NEUROLOGIC IMPAIRMENTS

Michael S. Lee, MD, Moderator

Leonard H. Calabrese, DO

Neil R. Miller, MD, FACS

Nancy J. Newman, MD

A CME activity provided by Evolve Medical Education LLC and distributed with *Practical Neurology* and *Retina Today*.

This continuing medical education activity is supported through an educational grant from Genentech.

evolve medical education

Distributed with

Practical Neurology®

RT Retina Today

Diagnosing and Treating Giant Cell Arteritis with Visual and Neurologic Impairments

Release Date: May 2018
Expiration Date: May 2019

FACULTY

MICHAEL S. LEE, MD, MODERATOR
Professor in the Departments of Ophthalmology, Neurology, and Neurosurgery, and
Mackall-Scheie Research Chair in Ophthalmology
University of Minnesota
Minneapolis, Minnesota

LEONARD H. CALABRESE, DO
Professor of Medicine, Vice Chair of Rheumatology,
Vice Chair of The Center for Vasculitis Care and Research,
R.J. Fasenmyer Chair of Clinical Immunology
Cleveland Clinic Lerner College of Medicine
Case Western Reserve University
Cleveland, Ohio

NEIL R. MILLER, MD, FACS
Frank B. Walsh Professor of Neuro-Ophthalmology and Professor of Ophthalmology,
Neurology, and Neurosurgery
The Johns Hopkins University School of Medicine
Baltimore, Maryland

NANCY J. NEWMAN, MD
LeoDelle Jolley Professor of Ophthalmology, Neurology, and Neurological Surgery
Emory University School of Medicine
Atlanta, Georgia

CONTENT SOURCE

This continuing medical education (CME) activity captures content from a roundtable discussion.

ACTIVITY DESCRIPTION

This document assesses the needs of ophthalmologists and neurologists to improve their skills in diagnosing, treating, and managing patients with giant cell arteritis (GCA). Patients with GCA have a range of symptomatic presentations, and no definitive diagnostic test exists. Rapid diagnosis and early treatment are critical to prevent irreversible blindness.

TARGET AUDIENCE

This certified CME activity is designed for ophthalmologists and neurologists with an interest in the diagnosis and treatment of GCA, along with the quality of life of patients with GCA, their family, and their caregivers.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- Recall patient risk factors and symptoms of GCA based on relevant classification and diagnostic criteria to confidently add GCA to a differential diagnosis.
- Distinguish among the visual abnormalities and ischemic events associated with GCA versus other causes.
- Formulate treatment options for patients with recently diagnosed GCA, including GC-sparing regimens and second-line therapy.
- Evaluate treatment options for patients with relapsing GCA and glucocorticoid-resistant GCA to determine if management is needed long term.
- Outline the underlying inflammatory processes involved in GCA.

- Outline the evidence for targeted therapy approved by the Food and Drug Administration (FDA), along with emerging therapies for the treatment of patients with GCA, including use as second-line therapy.

GRANTOR STATEMENT

Supported through an educational grant from Genentech.

ACCREDITATION STATEMENT

Evolve Medical Education LLC (Evolve) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

CREDIT DESIGNATION STATEMENT

Evolve designates this enduring material for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

TO OBTAIN AMA PRA CATEGORY 1 CREDIT™

To obtain *AMA PRA Category 1 Credit*™ for this activity, you must read the activity in its entirety and complete the Posttest/Activity Evaluation/Satisfaction Measures Form, which consists of a series of multiple choice questions. To answer these questions online and receive real-time results, please visit evolvemeded.com and click "Online Courses." Upon completing the activity and self-assessment test, you may print out a CME certificate awarding 1 *AMA PRA Category 1 Credit*™. Alternatively, please complete the Posttest/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC, 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950.

DISCLOSURE POLICY

It is the policy of Evolve that faculty and other individuals who are in the position to control the content of this activity disclose any real or apparent conflict of interests relating to the topics of this educational activity. Evolve has full policies in place that will identify and resolve all conflicts of interest prior to this educational activity.

The following faculty/staff members have the following financial relationships with commercial interests:

Leonard H. Calabrese, DO, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant*: Abbvie; Bristol Myers Squibb; Crescendo Bioscience; Genentech; Jansen; and Regeneron Pharmaceuticals, Inc.

Michael S. Lee, MD, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Grant/Research Support*: Quark Pharmaceuticals.

Neil R. Miller, MD, FACS, has no financial relationships with commercial interests.

Nancy J. Newman, MD, has had a financial agreement or affiliation during the past year with the following commercial interests in the form of *Consultant*: GenSight Biologics and Quark Pharmaceuticals. *Grant/Research Support*: Gensight Biologics and Santhera Pharmaceuticals.

EDITORIAL SUPPORT DISCLOSURES

Erin K. Fletcher, MIT, director of compliance and education, Evolve; and Katherine L. Molinar-Kimber, PhD, writer, have no financial relationships with commercial interests. Jaya Kumar, MD, peer reviewer, has no financial relationships with commercial interests.

OFF-LABEL STATEMENT

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The opinions expressed in the educational activity are those of the faculty. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

DISCLAIMER

The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of Evolve, *Practical Neurology*, *Retina Today*, or Genentech.

DIGITAL EDITION

To view the online version of the material, please visit go to evolvemeded.com/online-courses/.

evolve
medical education

Diagnosing and Treating Giant Cell Arteritis With Visual and Neurologic Impairments

Vision loss as a presenting manifestation of giant cell arteritis (GCA) is likely the only singular medical emergency in rheumatology. A less frequent manifestation is a cerebrovascular event, such as stroke. GCA affects people who are aged at least 50 years, and its diagnosis may become more common in ophthalmology and neurology practices as the aging population—the silver tsunami—increases in the United States. This roundtable discussion examines the importance and strategies of early diagnosis; symptoms and findings of visual and neurologic manifestations; pathophysiology of GCA; initial treatment strategies; strategy for managing patients' expectations; steroid-sparing strategies, including evidence for tocilizumab, recently approved by the Food and Drug Administration (FDA); and two distinct cases.

— Michael S. Lee, MD, moderator

GIANT CELL ARTERITIS

MICHAEL S. LEE, MD: When you see a patient with GCA, what sort of demographic information would make you say, "I'm concerned?"

NEIL R. MILLER, MD, FACS: First, you're talking about someone who has presumed GCA. Although Hispanics and African Americans are less likely to be affected,[1,2] that is an overall statistic.[3] My basic philosophy is that any elderly patient in virtually every racial group can have GCA.[1-3] The real issue is the age that someone can be and still cause worry about GCA. We are seeing GCA in patients 50 years or older. Certainly, I'm more concerned about the age of the patient than I am about the racial background.

NANCY J. NEWMAN, MD: I think that's a fair assessment. There is a higher prevalence among white women, particularly those with a northern Europeans/Scandinavian background.[1,2,4] However, anyone older than age 50, and certainly anyone more than age 60, can have GCA.[1-3]

VISUAL AND ISCHEMIC MANIFESTATIONS

DR. LEE: Let's discuss the various visual or neurologic consequences of GCA that each of you has seen. Consider starting with some of the more common conditions and move to the less common.

DR. NEWMAN: The most common ischemic complications of GCA would be symptoms like jaw claudication, which is ischemia of the chewing muscles. But from our bailiwick, the most common visual complications with GCA would be transient monocular vision loss and permanent vision loss (Table 1).[5,6] These complications are most often caused by anterior ischemic optic neuropathy (AION), with swelling in the front of the optic nerve and some posterior ciliary involvement. Additional complications may also include posterior ischemic optic neuropathy (PION), central retinal artery occlusion (CRAO), and choroidal ischemia, but *not* branch retinal artery occlusion (BRAO) (Table 2).[5,7] Transient double vision also can be the first symptom of GCA. Transient monocular vision loss and particularly transient double vision are symptoms patients should be asked about because they usually are not severe enough to indicate GCA diagnosis before there is permanent vision loss. A much smaller population of people can have cerebrovascular disease symptoms, including stroke (Table 3). The prevalence of stroke reported in one study was approximately 3% but ranges between 1.5% and 7% in patients with GCA.[5] This is typically a disease of extracranial arteries versus intracranial arteries.

DR. LEE: Are there other neurologic or nonneurologic presentations?

LEONARD H. CALABRESE, DO: GCA is a quintessential example of a disease that can be highly variable in its manifestations. There's huge channeling bias as to the type of practitioner who sees these patients. Dr. Newman has provided an excellent description of the disease symptoms we classify as head and neck ischemia.[8] The two other presentations of GCA are the systemic and inflammatory presentations that are largely polymyalgia rheumatica (PMR).[8] These painful, sudden-onset proximal muscular syndromes can be quite acute and very dramatic in onset. Systemic inflammatory symptoms and signs of GCA in approximately 40% or more of patients include fever, and 15% of these patients will have high fever and weight loss, as well as anemia of chronic disease. I've seen hemoglobin levels as low as 4 g/dL. In an elderly patient with this type of presentation, unless physicians are really thinking GCA, this

TABLE 1. COMMON VISUAL SYMPTOMS AND FINDINGS IN PATIENTS WITH GCA.[5]

Common visual symptoms	Common ocular findings
• Transient monocular vision loss • Permanent vision loss • Transient double vision • Persistent double vision	• AION • CRAO

Abbreviations: AION, Anterior ischemic optic neuropathy; CRAO. central retinal artery occlusion; GCA, giant cell arteritis.

TABLE 2. LESS COMMON VISUAL FINDINGS IN PATIENTS WITH GCA.[5]

Less common visual symptoms	Less common ocular findings
• PION • Choroidal ischemia • Third nerve palsy • Fourth nerve palsy • Sixth nerve palsy • Nonspecific ophthalmoparesis	• Cotton wool spots • Homonymous field defects • Cortical blindness

Abbreviations: GCA, giant cell arteritis; PION, posterior ischemic optic neuropathy.

TABLE 3. CEREBROVASCULAR EVENTS OF GCA.[5]

Strokes and transient ischemic attacks	Predictors for subsequent ischemic event
• Occur in 1.5% to 7% of patients with GCA	• Previous ischemic event in patient with GCA
• Caused by occlusion or stenosis of extradural vertebral or carotid arteries	• Traditional cardiovascular risk factors and lower inflammatory responses

Abbreviations: GCA, giant cell arteritis.

disease can go undetected in the workup algorithm for quite a long time.[2] More recently, however, the large-vessel presentations are being recognized.[2] Although the vast majority of people with GCA have large-vessel involvement with granulomatous arteritis, most are asymptomatic. Limb ischemia is very rarely due to dissection. And, as Dr. Newman mentioned, involvement of the extracranial vasculature can also occur. This is a disease of large muscular vessels with vasa vasorum. So, all of those presentations can be seen.

DR. LEE: Great. What sorts of things do you like to ask in your review system? How do you tease out that jaw pain?

DR. MILLER: In fact, some physicians request patients do a so-called chewing gum test. Patients are given chewing gum and asked to report their level of discomfort when they chew. Many of these patients have been treated for several weeks—or even months—for temporomandibular joint (TMJ) pain. Secondly, I agree with Dr. Calabrese, as I want to know about fevers of unknown origin. Another interesting manifestation of GCA is chronic cough. Dr. Newman mentioned the issue of transient obscurations of vision. These can be identical with those that we usually associate with cardiac disease or carotid disease. Patients may have not only transient double vision, but permanent double vision from either extraocular muscle ischemia or ocular motor dysfunction.[5] I also want to know about fatigue and weight loss. These are some of the prominent symptoms and signs noted among these patients.

DR. NEWMAN: Regarding causes of persistent vision loss in GCA, AION is by far the most common permanent visual manifestation of the disorder, and PION is very rare.[5] However, if a patient presents with PION, and he or she is not in the perioperative period of spine surgery or coronary artery bypass grafting (CABG) surgery, then GCA should be the top 9 out of 10 on your list for causes of PION. So, even though it is uncommon, if you believe a patient has PION, then you need to be suspicious of GCA.

DR. MILLER: I think that PION is a really important issue. Many physicians, particularly ophthalmologists, are aware that AION occurs. When someone comes into your office with decreased vision and the fundus looks perfectly normal, I think many ophthalmologists may relax and decide it's not GCA, when in fact it could be.

DR. LEE: Thank you. Let's review what we know about the pathophysiology of this disease.

PATHOPHYSIOLOGY

DR. CALABRESE: This disease, at the tissue level, affects large vessels that have internal elastic lamina and vasa vasorum. The immunologic basis of this disease involves perturbations of both innate and adaptive immunity. GCA is associated with sequential phases of immunoregulation, although they are not completely linear.[9] The initial phase corresponds to immunopathologic involvement of the adventitia. Dendritic cells and T cells are recruited and activated. A second phase is a spread of this inflammation to medial intimal anatomic spaces associated with macrophage activation, along with enhanced cytokine release. Moving ahead, changes may occur, including rises in granulomatous inflammation, and about 50% of people will actually display giant cells. Finally, a stage of neointimal fibroplasia or neointimal fibrosis can be observed. Depending on the patient's presentation and when she or he is biopsied, you may see something very different. Pivotal cytokines are T_H-1 derived cytokines including gamma interferon and IL-1 and IL-6 from activated macrophages. T_H-17–derived cytokines include IL-17, IL-21, and IL-22.[10] IL-6 is pivotal in this process because it's involved in differentiation of T_H-17 cells. More recently, the role of IL-21 has been proposed by several laboratories as being a possible master switch.[10,11] Collectively, this is a broad level of immunodysregulation involving multiple limbs of the integrated immune response.[10] I have not talked about etiology, but just immunopathogenesis. I wish I knew what caused this.

DR. MILLER: What do you think about the theory that varicella zoster virus (VZV) is an etiologic agent?

DR. CALABRESE: Well, you're asking the right guy. But only

because Donald H. Gilden, MD, from the University of Colorado School of Medicine's Department of Neurology, was a very dear friend of mine.

DR. MILLER: Mine, too.

DR. CALABRESE: I knew his data supporting the role of VZV in GCA extraordinarily well.[12,13] I really respect his work. Yet, we have made herculean efforts to duplicate his finding of VZV in GCA specimens versus normal temporal artery biopsies. We,[14] and several other groups,[15] have been unable to verify a widespread and ubiquitous association as proposed by Dr. Gilden and Maria A. Nagel, MD, from the University of Colorado. I am sure that a few cases are VZV-driven, but it's not a universal relationship.[16] Several years ago, our collaborators wrote the positive articles, and we were the ones who wrote the negative articles, including previous reports of indicated infections from parvovirus B19 to mycoplasma to varicella.[17] Everything about GCA supports an infection-driven disease, yet no single pathogen has fulfilled any type of postulates to prove this. An interesting recent study by Peter A. Merkel, MD, MPH, from the Penn Institute of Immunology at the University of Pennsylvania's Perelman School of Medicine, looked at antecedent infections in patients who ultimately developed GCA during a period of 5 or 10 years.[18] In this appropriately controlled population, the GCA group had many infections, including zoster, but also other infections of varying degrees of severity. I think it may represent some sign of immunosenescence.[18] I'd love to hear your insights.

DR. MILLER: We've also looked in a very limited way and been unable to confirm VZV. Drs. Gilden and Nagel suggest that perhaps we are not doing it correctly because they do all of these 5 µ step-sections and really go through hundreds of them, which we have not.

DR. CALABRESE: We have surgically preserved snap-frozen aortas, where we merely took large pieces, homogenized them, then analyzed them using polymerase chain reaction (PCR), and we saw no signal.[14] We can't beat PCR technique in terms of a shotgun search for VZV.

DIAGNOSIS

DR. LEE: Let's move the discussion to diagnosis. What lab tests do you order, and what would you consider to be an abnormal test?

DR. NEWMAN: I went through a fibrinogen phase, but I'm not there anymore. I usually order a complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels. I use the CBC results combined with hemoglobin level in the hematocrit to interpret the meaning of the ESR. The CRP is a slightly faster acute phase reactant than the ESR. Sometimes I request these tests to cover myself and expect them to be normal. Sometimes, I am very, very suspicious, and even if the markers do not come out particularly abnormal, I am still highly suspicious. So, a certain number does not mean anything to me. I have to see it in the complete clinical setting.

DR. LEE: Dr. Miller, what do you like to use in terms of an acceptable range of an abnormal test result or a threshold for an abnormal test result?

DR. MILLER: I agree with Dr. Newman in terms of getting a CBC with platelet count, ESR, and CRP. I use the namesake "Miller criteria" of: the age divided by 2 for men, and the age plus 10 divided by 2 for women.[19] No class I data tell us what a really abnormal ESR is, but that is a good benchmark. We, and others, have found that about 2% to 3% of patients with biopsy-proven GCA will have both a normal ESR and a normal CRP level.[20,21] But the vast majority of patients with GCA (about 98%) will have an abnormal result, either one or the other, or both.[20,21] I think GCA, just as Dr. Newman suggested, is a clinical diagnosis. But I think most patients will have an abnormally elevated CRP or ESR. I'd be interested to know what Dr. Calabrese's experience is as a rheumatologist, but in my experience, only about 60% of the patients with biopsy-proven GCA have a thrombocytosis.

DR. CALABRESE: I agree with the previous comments and think that acute phase reactants certainly have more and higher negative predictive value than positive predictive value because they are very nonspecific inflammatory markers, as everyone appreciates. ESR is very difficult to interpret in people more than age 75 to 80 years, as you pointed out. CRP is really an interesting test, and let's revisit it in a little more granular fashion. We were among the first institutions to routinely use CRP in the hospital many decades ago. At that time, we looked for healthy people to find out the normal levels. Thirty years ago, the normal CRP level was 20 mg/L. It was insane, as this level is very elevated. Over time, healthy levels went to 10 mg/L, then 8 mg/L, and now 6 mg/L. Ultrasensitive CRPs have a range approaching 0.5 mg/L to 3 mg/L. I cannot find any report of a patient with GCA with a CRP level of less than 3 mg/L. I've never seen, in our institution, anyone with a CRP level of less than 5 mg/L. And while these may be in your normal range, this is where I will keep the heartbeat alive of GCA diagnosis, depending upon the pretest probability. So, physicians should look at the number and combine it with clinical symptoms. The platelets and alkaline phosphatase are elevated in a percentage of GCA patients, but I put my money with CRP. I obviously do an ESR. That's how I use it.

DR. LEE: I agree about the clinical diagnosis. As a general rule, just like the Miller rule for ESR, I like to use the normal for the laboratory on the CRP level because the normal value seems to vary quite a bit, depending on the hospital laboratory.

DR. MILLER: I was under the impression that we should not get ultrasensitive CRPs and that they are useful in cardiac disease, but not in GCA. Is that wrong?

DR. CALABRESE: No, you are exactly right to obtain a standard CRP. I'm just pointing out that the lens of CRP has changed over the years. We now recognize that a CRP level between 3 mg/L and 6 mg/L probably represents a slightly activated CRP. This level is at the high end of the ultrasensitive CRP tests and at the very low end of a traditional CRP level in most labs.

Above 6 mg/L is clearly abnormal. I would say 99% of people with GCA will have elevated CRP.[20] We're wringing our hands over the 1%, but that is what makes things interesting.

DR. LEE: So, I'd like to ask all of you whether you obtain either a temporal artery ultrasound, cranial MRI, or large-vessel imaging within the chest to determine a diagnosis of GCA?

DR. NEWMAN: In preparation for this discussion, I pulled some review articles from major journals. They are written by the same clinicians over and over again, and the clinicians are from mostly outside the United States.[22-24] They are very hot on ultrasound of the temporal arteries as a diagnostic maneuver to look for the halo sign. I am not going to trash the idea, but I have not really been exposed to it and do not use it. My feeling is that we would still get a temporal artery biopsy (TAB) regardless of the ultrasound results.[25] Regarding the aorta, we were imaging the aorta more from interest than for diagnosis or guiding our management. Certainly, we have not been using ultrasound.

DR. MILLER: I only use ultrasound if I am concerned that a branch of the temporal artery is feeding the intracranial circulation. I don't use it for diagnosis, nor do I use high-resolution MRI. Although, like Dr. Newman, I'm aware of the changes that you can see in these very high-quality MRIs. We do order a CT of the chest when we are worried about aortitis. Aortitis is rare in the population I've seen, but I know it is talked about a lot. As an ophthalmologist or neuro-ophthalmologist, we get patients who have vision loss. Once we make the diagnosis with clinical symptoms, signs, and laboratory results, and then do a TAB, we send these patients to our friendly rheumatologists. The rheumatologists usually order the imaging of the chest.

DR. LEE: Just to clarify, you would not obtain a chest CT for diagnostic purposes for GCA but to look for evidence of widespread disease?

DR. MILLER: Correct.

DR. LEE: Great. And Dr. Calabrese, do you order any of these other noninvasive imaging tests?

DR. CALABRESE: This is kind of a "blind man and the elephant" approach. Certainly, unilateral TAB is our standard approach to securing a GCA diagnosis. The prospect of temporal artery ultrasound is very alluring. I know these data very well. As Dr. Newman said, Europeans have been using point-of-care ultrasound for many years. At Cleveland Clinic, I cannot get high-quality point-of-care vascular ultrasounds. Interestingly, the halo sign is much more liable to early interventional therapy (glucocorticoids) than histology. At centers like ours or the Mayo Clinic, we use the TAB. I'd be interested in using more ultrasound, but I don't. I think large-vessel imaging is of increasing importance in this disease, probably not as much to ophthalmologists and neurologists as to rheumatologists because large-vessel involvement is very common. If PET/CT scans are performed on people with GCA, 70% have large-vessel involvement. These results do not influence their therapy—I'm just providing some epidemiology. Secondly, a population of patients with GCA do not have head and neck ischemia and may present either with a fever of unknown origin or inflammatory disease of unknown origin. Some individuals just have high ESR or CRP levels. They don't have jaw claudication, visual symptoms, nor headaches. These are the people for whom large-vessel imaging can be highly effective.[26] GCA is really a great disease for interprofessional collaboration, and patients receive it here and at places like Emory University, Mayo Clinic, and Johns Hopkins University. We all have a slightly different perspective. I think there's utility to all of these tests.

DR. LEE: In summary, you are not using these noninvasive imaging tests, such as ultrasound and cranial MRI, for diagnosis. But in Europe, these imaging tests are frequently used, as described by Monti and colleagues.[22-24]

DR. CALABRESE: Cranial MRI is a more complex issue. You need a 3 Tesla or higher machine. Vascular imaging is of interest, but it has not been studied nearly as much as temporal artery ultrasound. There have been multicenter randomized controlled trials comparing TAB and ultrasound results,[27] but not vascular imaging by MRI. Large-vessel imaging, such as CT and MR of the chest and body, is a different story. That is very valuable.

DR. LEE: I agree. Dr. Miller, can you tell us about TAB and some of the issues surrounding it?

DR. MILLER: First of all, I believe strongly that even if the clinical picture is typical for GCA, patients should have a confirmatory biopsy. Over the years, I have seen too many patients who had a clinical diagnosis, which was fine, but treatment questions arose later. For example, after they put the patient on steroids, the patient developed side effects or hip necrosis, and sooner or later, a physician says maybe the patient did not have GCA after all. Everybody wonders, but after they take the patient off the steroid, the patient goes blind, has a heart attack, or a stroke. So, I think it is very important to obtain the histopathologic data.

As far as TAB, Len mentioned the issue of a unilateral biopsy, and I'd like to suggest consideration of bilateral biopsies. Some degree of discordance in GCA positivity is seen between the two sides.[28-30] Wills Eye reported at 1% discordance,[31] our clinic at Johns Hopkins found 7% discordance[32] and Mayo Clinic found 11% discordance.[33] Thus, my preference for a patient who presents with vision loss,

unilateral visual loss, or unilateral diplopia, is to do a biopsy on that side but prepare the patient for a bilateral biopsy. If the first biopsy specimen appears abnormal at the time of surgery, then I won't operate on the other side. If it appears normal, I will do a bilateral biopsy. I think when the biopsy is performed correctly, there is very little morbidity. The biggest issue arises if the surgeon makes the incision perpendicular to the vessel, which increases the danger of cutting some facial nerves. Until the nerves regenerate, the patient has numbness in the area of the biopsy. But if you incise along the path of the artery, which I typically either palpate or use ultrasound to identify the vessel and its path, it is a pretty straightforward procedure. Even though there are skip areas of normal pathology, a TAB of only a couple of millimeters has a ~90% chance of identifying an abnormal vessel.[34] I, like many of my colleagues, like to excise a couple of centimeters.[35,36]

DR. LEE: Thank you. Dr. Newman, could there be a biopsy-negative GCA diagnosis? The pathology will indicate "healed" arteritis or evidence of "healed" arteritis. Can you comment on those?

DR. NEWMAN: First, there can be a biopsy-negative GCA diagnosis. To me, it really depends on the pathologist's expertise. We are very lucky to have one of the best ocular pathologists at Emory, Hans E. Grossniklaus, MD, MBA, who has a big interest in GCA. I really trust his judgement. If he believes that the TAB reveals only atherosclerosis and no signs of GCA, then I believe it is negative. Conversely, if he tells me it is not positive for a florid lumen, but it probably was at some point, I accept his interpretation. I know there is much controversy about the issue of "healed" arteritis, but if he tells me there's "healed" arteritis, I agree.

DR. MILLER: In the 1980s, we did a study at Johns Hopkins in which an ocular pathologist, William Richard "Dick" Green, MD, plus two general pathologists, and an intern in pathology, looked at and rated specimens as acute arteritis healed or negative, meaning either normal or atherosclerotic.[37] We found discordance among the pathologists: once they agreed on specific criteria (eg, fragmentation of the elastic lamina with evidence of old inflammation/fibrosis), there was significant concordance in terms of making a diagnosis of healed arteritis.[37] I think if you have a pathologist who is experienced in interpreting fragmentation of the elastic lamina with no acute process, then I think it is absolutely worthwhile. As Dr. Calabrese said, giant cells are present in approximately 50% of GCA samples. Although we call the disease GCA, the pathologist does not have to find actual giant cells for its diagnosis.

DR. CALABRESE: I totally respect your opinions, and here there may be a small parting of the ways. The issue of healed arteritis is a vexing one. More recent studies have been conducted to critically appraise these data and look at them in the context of age- and sex-matched controlled patients. My appraisal of these data is that I just don't accept healed arteritis in patients who don't have GCA and have never been treated for it. Separating the histopathology of the aging artery from GCA-associated fragmentation of the internal elastic lamina, fibrointimal thickening, and intimal fibrosis are very tough calls. However, I have also seen more than my share of patients with healed arteritis. Pretest probability influences me greatly, and a study by Carlo Salvarani, MD, and colleagues from Italy has shown that at least the majority of these cases probably are not healed arteritis.[38] Isolated involvement of the vasa vasorum occurs in only a small group, and I consider them active arteritis.

DR. MILLER: I agree with you completely. The issue of healed arteritis is somewhat like seronegative Lyme disease: it's contaminated by many overcalls. These normal aging changes that are commonly characterized as healed arteritis have obscured the fact that some individuals with typical signs and symptoms of GCA do, in fact, have healed arteritis. Combining the clinical history, findings, and laboratory studies all together with the pathologist's report of vasculitis in the proper setting, I'm comfortable treating the patient for GCA and referring them to the rheumatologist.

DR. LEE: I feel like I have to weigh in here. I view this scenario like a borderline result with neither 100% positive nor 100% negative certainty. You use the pretest probability to help make a decision about whether to treat or not to treat.

Changing subjects, Dr. Newman, as a neurologist, should neurologists think about GCA every time that they see vertebrobasilar ischemia in the elderly?

DR. NEWMAN: That's a tough question. The prevalence rate is less than 3% of GCA patients with strokes,[5,39] and we have so many stroke patients. Of course, everyone who is older than 50 years and has a neurologic event is going to have a CBC, ESR, and CRP performed. Except for vision loss, I do not think GCA comes up in a neurologist's mind when patients are presenting with strokes.

DR. MILLER: Dr. Newman, why would they all get an ESR and a CRP if physicians are not concerned about a vasculitis of some sort?

DR. NEWMAN: Why do patients all get tested for B_{12} levels?

DR. MILLER: Fair enough.

DR. NEWMAN: I think if the ESR and CRP levels come back high, that is going to trigger the possibility of GCA diagnosis. Unlike a classic presentation of AION with a borderline ESR and CRP that you know is GCA, in cases like vertebrobasilar ischemia, I believe physicians probably have to be pushed by high CRP and ESR levels to think of GCA.

DR. MILLER: One issue that often comes up, both with respect to stroke and ischemic optic neuropathy, is the elderly patient with diabetes. The patient may have a little fatigue, a minor headache, and temple pain. How high can an elevated ESR be from diabetes alone? Dr. Calabrese, what are your thoughts about that? Does it matter?

DR. CALABRESE: That's a great question. Because the epidemiology of stroke and GCA shows that the actual GCA incidence is influenced by additional cardiovascular risk factors, the diabetic, hypertensive, hyperlipidemic patient with GCA is much more likely to be a stroke patient statistically than not. Diabetic renal involvement increases the risk. Concurrent diabetes makes it much more difficult to interpret 35-mm to 45-mm ESRs.

DR. NEWMAN: I think your insights are actually extremely important because I'm surprised that vascular risk factors are not more important in a stroke resulting from GCA. If the pathophysiology is inflammation of the vessel wall, which leads to closing off the lumen, I would think that diseases which have caused luminal sclerosis and narrowing are the ideal risk factors. It's fascinating that the GCA patients with really elevated ESR and CRP don't have the highest risk for ischemic complications both in the eye and the brain. Instead, the patients with moderate elevation of ESR and CRP have the highest risk.[40]

DR. CALABRESE: This interesting epidemiologic observation has really no good explanation. Maria C. Cid, MD, said patients with the most robust inflammatory responses are also making vascular endothelial growth factor (VEGF) and vascular remodeling factors. These factors may theoretically protect these vessels from occlusion. It's an important observation.

DR. MILLER: Also, many of these patients are on statins for hypercholesterolemia, and as Dr. Lee said, this borderline elevated or high-normal ESR in a patient with a statin may be a false-negative.

TREATMENT

DR. LEE: I'd like to move on to treatment.[41] Let's discuss how you treat patients with GCA with vision loss or without vision loss?

DR. MILLER: When a patient has vision loss, I recommend high-dose IV steroids, methylprednisolone 1 g/day for at least 3 days. There are no class I data, as far as I know, on this treatment. Although many rheumatologists would argue that low-dose oral prednisone is well absorbed from the gut, and that there's no reason to give methylprednisolone, Grant T. Liu, MD, Bascom Palmer Eye Institute, and his colleagues showed a few years ago that only the patients who received high doses of steroids had stabilization of vision, a few had return of vision, and fewer had attacks in the opposite eye.[42] Colin Chan, MBBS, FRANZCO, and Justin O'Day, MBBS, FRACS, FRACP, FRCS, FRACO, FRCOphth, in Australia confirmed that high-dose IV methylprednisolone was more likely to prevent visual loss in the opposite eye than treatment with low-dose oral prednisone.[43] The 2010 British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) guidelines also suggest 250 mg to 1000 mg methylprednisolone IV for 3 days initially in patients with vision loss.[44] I use the same regimen for patients with diplopia and strabismus who have biopsy-proven or suspected GCA. I don't treat the patients who have no visual symptoms. Rheumatologists or the internists will refer them to me for the biopsy and to see if there are any changes in the fundus, cotton wool spots, or other evidence of ischemia. If there are none, then the patient returns to them and they decide the treatment based on the clinical picture.

DR. LEE: Dr. Newman and Dr. Calabrese, any other thoughts on acute treatment of GCA?

DR. CALABRESE: From our perspective, vision loss in GCA as a presenting manifestation of GCA is the only singular medical emergency in rheumatology. I agree 100% with your treatment, and I think you've nicely phrased the inadequacy of the data. We use the same algorithm of IV methylprednisolone for 3 days. But I think timing of treatment is more important than route of administration, (ie, IV or oral). I mean not tomorrow, but eat this prednisone right now in my office. Then we'll figure out what we are going to do. In the absence of visual symptoms and particularly the absence of head and neck ischemic symptoms, then oral therapy is the gold standard, and how you dose is kind of handwaving.

DR. MILLER: I agree completely. Once I make a diagnosis of presumed GCA, that patient doesn't leave without steroids (either IV methylprednisolone or oral prednisone). We are fortunate to have a large group of oculoplastic specialists who now do most of the biopsies. Although we can do the biopsy within 24 hours, we never wait to place the patient on steroids, even for 24 hours. They go on steroids right away.

DR. CALABRESE: Because this is a teaching forum, and the vast majority of patients are not going to get a biopsy in 24 hours, I think we have to emphasize and re-emphasize the need for a prompt, presumptive therapy for patients with presumed visual loss from GCA.

DR. MILLER: I agree 100%.

DR. NEWMAN: In a nice point/counterpoint article in the *Journal of Neuro-Ophthalmology* between Sohan Singh Hayreh, MD, MS, PhD, DSc, FRCS, FRCOphth (for oral steroids), and Valérie Biousse, MD (for IV steroids),[45] the bottom line was that they both actually agreed: hit it hard and fast. I agree.[46]

DR. MILLER: There are a few articles on using heparin as an acute adjunctive treatment. Sometimes, it seems to work. Lawrence M. Buono, MD, and colleagues had a case where the patient was losing vision in both eyes, was treated with heparin, and regained vision associated with improvement in blood flow in the posterior ciliary arteries.[47] But we don't anticoagulate routinely.

DR. NEWMAN: Do you put these patients on aspirin?

DR. CALABRESE: I give low-dose aspirin for the first 2 weeks.

DR. MILLER: We put them on aspirin at a dose of 81 mg/day. But we don't put them on heparin.

DR. LEE: We also put them on aspirin because we found that patients with GCA who received aspirin were less likely to experience ischemic complications compared with those who were not on aspirin.[48]

DR. CALABRESE: One of the most profound and severe complications of GCA is progressive vertebrobasilar syndrome. I have seen several of these during my career. It's a terrible disease despite whatever you do—heparin, steroid pulse—to salvage them.

DR. MILLER: I tell patients who've lost vision in one eye that we are going to attempt to prevent visual loss in the other eye. But I never tell them that treatment is going to prevent it. About 10% of patients will go on to lose vision in the opposite eye, despite treating them with high-dose IV or oral steroids. And those patients are the ones in retrospect, Dr. Newman, that maybe they should have been anticoagulated. But who knows at the time, maybe ultrasound will show us that.

DR. LEE: How quickly would you expect a patient with headache or double vision to improve and/or symptoms resolve once he or she is taking high-dose oral prednisone?

DR. MILLER: I've seen it occur within 24 hours. We have patients whom I've seen late in the evening, or late in the afternoon, brought them into the hospital, and put them on steroids. When I see them the next morning, they can't believe how much better they feel.

DR. NEWMAN: Simmons Lessell, MD, used to tell a wonderful story about an elderly woman in the hospital for fever of unknown origin. She was given her neighbor's prednisone by mistake and within 2 hours she felt fabulous. If a patient's headache does not improve with high-dose steroids within 24 hours, I would rethink the diagnosis.

DR. MILLER: I agree. I've had patients who were sent to me on oral prednisone, and they still had a lot of symptoms. I did the biopsy, put them on higher dose intravenously, and their headache went away and they felt better. Now, I grant you that everybody feels better on steroids, but I really do believe there is a difference between the standard dose (40 mg/day to 60 mg/day) and a high dose (500 mg/day to 1,000 mg/day for 3 days) followed by a standard dose in those patients who have significant symptoms.

STEROID-TAPERING REGIMENS

DR. LEE: That's great. Dr. Calabrese, how do you taper the steroids? Over what period of time? Do you remove the steroids altogether, or do you keep these patients on low-dose steroids for many years?

DR. CALABRESE: That's a great question, and we need some handwaving here. I think that all of us would maintain a high dose of steroids whether it is prednisone at a dose of 1 mg/kg daily or 60 mg of prednisone for at least 2 weeks. For those patients who don't have ocular symptoms and are lighter weight, we may use 40 mg. If a patient is on 60 mg or 80 mg prednisone, probably at 2 weeks, we might start slowly tapering the steroids by no more than 10% every week or 2 weeks. By 3 months, the treatment dosage should be in the 10 mg to 20 mg range. Considering that patients' symptoms are decreasing, then if I have the opportunity to see them, I like to check the acute phase reactants to determine if they are being suppressed. Subsequently, we taper treatment to 10 mg prednisone.

Subsequently, the tapering gets slower. We are tapering by 10% or 1 mg every 2 weeks. The endpoint of the tapering is really uncertain. Fewer than 1 of 3 people will be off steroids by the end of 1 year.[49] That means that 2 out of 3 patients with GCA will probably be on some low dose of prednisone. Among them will be people who have flared (Table 4). The rate of flaring, which is fortunately nonvisual flaring, such as headache, constitutional symptoms, or polymyalgia, varies and depends on the patients and tapering series. Eliminating steroids from a treatment regimen is really an inexact science. The studies at the large referral centers like Cleveland Clinic and Mayo Clinic report that the median duration of steroid treatment is approaching 3 years.[49] Patients will be on glucocorticoids for the long haul, and physicians must be vigilant for exacerbations and remissions. Fortunately, if the patient does not have visual loss during the first few weeks, the prognosis is quite good for the eyeball.

TABLE 4. INCIDENCE OF COMMON RELAPSES.

Relapse or flare symptom or finding	Percent of GCA patients
PMR symptoms, such as arthralgia	33-63%[50,51]
Cranial symptoms (eg. new headache, tenderness of jaw, jaw claudication)	28-42%[50,51]
Elevated ESR and CRP	79%[52]
Malaise and new fatigue	20%[50]

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; PMR, polymyalgia rheumatica.

DR. MILLER: Agreed.

STEROID-SPARING REGIMENS

DR. LEE: That brings us to corticosteroid-sparing agents. Do you use them? I'd like to discuss tocilizumab (TCZ), which was approved by the FDA in 2017 for the treatment of GCA. Do you use the other steroid-sparing agents, which are off-label use?

DR. CALABRESE: I'd be happy to address this. This is near and dear to my heart. Before the recent approval of TCZ, we have had very poor steroid-sparing regimens available to us. We have been participants in the multicenter methotrexate trials.[53] Even with a

meta-analysis,[54] if it does work,[55] it doesn't work very well. There are very few options for those people who could not taper below 10 mg/day to 15 mg/day of prednisone, but methotrexate (MTX) was just not effective.[53] Other agents, azathioprine, infliximab, and beyond, showed the same results.[56] Some patients treated for GCA during a 12-month period have received a total of 3,000 mg to 4,000 mg of prednisone.[57] For people in this age group, with comorbidities such as osteopenia, osteoporosis, diabetes, glaucoma, and all the other attendant cosmetic aspects of steroids, this is very serious business. The steroids, after a while, are the major contributors to the loss of quality of life.

DR. MILLER: I agree. We have used MTX and have found that it's hit or miss. I've definitely seen some patients who've appeared to respond to MTX, but also a lot of patients in whom MTX just did not work at all. That's why we are so excited about TCZ.

IL-6 is a big player in GCA. This monoclonal antibody, TCZ, targets IL-6 and appears to reduce the dependence on steroids and reduce the recurrences of or exacerbations of the disease.[57] I'd be interested in Dr. Calabrese's thought about using it as a primary agent. The articles from the Swiss[58] and GiACTA trials[57] did not address that. But certainly, the elephant in the room is whether you could treat entirely with TCZ and forego steroids.

DR. NEWMAN: I'd love Dr. Calabrese to talk about the serious adverse event that happened in the TCZ group. One patient developed AION during a flare; the patient was in the low-dose group receiving TCZ every other week.[57] Becaise IL-6 affects angiogenic activity, we may need to cautiously consider its effects on people with ischemic complications.

DR. CALABRESE: I think TCZ has a profound effect on this disease. It has been used with glucocorticoids. It is given subcutaneously every other week. There are two dosing regimens, and both of them were highly effective. The high-dose (162 mg given as a weekly subcutaneous injection) was more effective than the low-dose (162 mg given every other week as a subcutaneous injection),[57] but both dramatically showed a fourfold higher primary endpoint (sustained prednisone-free remission at week 52),[57] in patients who were completely relapse-free from week 12 to 52. The reduction of glucocorticoids was profoundly dramatic. Overall, the toxicity was pretty minor. I was mostly concerned about lower gastrointestinal (GI) perforations, which are part of the IL-6 spectrum of complications in rheumatoid arthritis, based on much data.[59] We saw no GI perforations in the GiACTA trial,[57] and patients were probably screened for it. Serious infections were more common in patients on glucocorticoids[57] because they are getting more glucocorticoids. The quality-of-life data in this study were the most remarkable thing for me: not only did the patients taking TCZ at 52 weeks have statistically and clinically meaningful higher quality of life, as measured by SF-36 than the group taking glucocorticoids, but they palpably had higher indices of quality of life than age- and sex-matched controls who did not have GCA.[57] It's comparative. So, it makes us think: IL-6 is very central in terms of regulating sleep, pain, and potentially mood.

Regarding use of TCZ as monotherapy, there have been some small trials using it as monotherapy in PMR.[60,61] While it is effective, it is not as quickly as effective as glucocorticoids in PMR. By extrapolation—and I don't know the optimum regimen—possibly a very brief induction with glucocorticoids and then TCZ maintenance may be important. But I think that until someone can prove to me otherwise, if I had a patient with threatened vision, I would use glucocorticoids to cool down the GCA and then transition to TCZ. That's just the way I'm thinking about it.

DR. MILLER: To clarify about the adverse event Dr. Newman bought up, most of the visual flares in the GiACTA trial were in the placebo plus steroids groups. No patient in the weekly TCZ group had any visual flares at all.[57] One patient in the group given TCZ every 2 weeks had an ischemic optic neuropathy, as well as some PMR symptoms.[57] Overall, they did well.

DR. CALABRESE: The GiACTA trial included 149 patients treated with TCZ + steroids,[57] and there was one visual loss. That is pretty remarkable.

DR. MILLER: I agree completely.

DR. NEWMAN: Although there was no permanent vision loss in the other groups.

DR. MILLER: That's correct. They had blurred vision and amaurosis fugax.[57] And as I recall, even the ischemic optic neuropathy turned out not to be severe.[57]

DR. LEE: Completely reversible is what I understand.

DR. NEWMAN: Are you using TCZ right now?

DR. MILLER: Absolutely.

DR. NEWMAN: Because our rheumatologists are anxious about it. They're not buying in quickly.

DR. CALABRESE: We are using TCZ, but I don't want to imply that all our vasculitis team members are treating everyone with TCZ. In general, glucocorticoids are the standard bearer, and that is the therapy, especially for younger, more robust patients who are not confounded by comorbidities, particularly in the absence of major complications. But patients with osteopenia, diabetes, hypertension, dyslipidemia, and other vasculopathic complications are those who I truly want to use TCZ to treat GCA. Although I'm making a case that glucocorticoids are the way to go, the third setting is if I or my wife had GCA, or friends, I can tell you what the results would be.

DR. MILLER: If they can afford it.

DR. CALABRESE: You need patients who will not buckle to that. TCZ provides 4 times the remission rate and reduces the complications. So, it is not like a tough sell.

DR. NEWMAN: Are insurance companies paying for it?

DR. CALABRESE: Absolutely. It has much less blowback than we expected. Actually, I have seen none myself, and I've talked to a group who treats more patients than I do. That is not an issue.

DR. MILLER: Yes. I agree.

DR. LEE: Especially since it is now approved by the FDA.

CASE HISTORIES

DR. LEE: Let's move on to discuss the cases. The first case is a patient with transient vision loss, and the second case is a patient with binocular double vision. Let's take a look at the history and physical and make some comments on that first case.

CASE 1

A white man, age 68, developed episodes of transient vision loss in his right eye during the past 3 days. It has occurred 4 times and lasted 3 to 6 minutes each time. This was not associated with pain, and his vision returned to normal afterward. As a young man, he would have zigzag lines across vision in both eyes, with gradual worsening and then gradual improvement during the course of 30 to 40 minutes. These have occurred many times over the years, with the last episode about a year ago. He denies double vision, headache, weakness, numbness, ataxia, facial droop, and dysarthria.

PAST OCULAR HISTORY

- Cataract extraction left eye (OS)
- Glaucoma both eyes (OU)
- Cataract right eye (OD)

PAST MEDICAL HISTORY

- Hypertension
- Seizures
- Restless leg syndrome
- Heart attack at the age of 51 years status post stenting and bypass surgery
- Cardiac ablation for an arrhythmia

MEDICATIONS

- Pramipexole
- Metroprolol
- Levetiracetam
- Alprazolam
- Brimonidine
- Aspirin

ALLERGIES

- Gabapentin
- Statins
- Carbamazepine
- Sulfa antibiotics

SOCIAL HISTORY

- He denies smoking and use of alcohol.

REVIEW OF SYSTEMS

- Headaches for the past 2 months
- 10-lb weight loss during past 2 months but has been dieting
- Difficulty sleeping for years
- Temporomandibular joint disease
- Urinary frequency from benign prostatic hyperplasia
- Anxiety

EXAMINATION

Visual acuity	20/20 OU
Pupils	Equal and normal
Intraocular pressure	15 mm Hg OD, 13 mm Hg OS
Eye motility	Full, normal alignment
Visual fields	Normal to confrontation and formal perimetry
Color vision	Normal OU
Slit lamp exam	Cataract OD, Intraocular lens OS
Fundus exam	Slight cupping OU

DR. MILLER: I thought the first case was fascinating because I don't know that I would have thought of GCA in this patient. The only thing he had going for him was that he was age 68, and he was being treated for so-called TMJ disease. He reported a history of headaches, and the transient vision loss could have been due to migraines or an amaurosis fugax from atherosclerosis. This case is a great example of even visual protean manifestations. Obviously, it's crucial to take a thorough history, because if you stick with the past medical history of hypertension, heart attack, and cardiac ablation, you could get lost in the "he's entitled to some headaches" thought process. He's got TMJ pain, well, perhaps he does. It was a very frightening case to me because it gives you an idea of how a patient with GCA can present with amaurosis fugax that not only is amaurosis fugax, but it is an amaurosis fugax with positive phenomena suggesting more of a vasospastic disease than of a vaso-occlusive one.

DR. NEWMAN: I don't think his transient vision loss itself has caused this phenomenon. I think he had a history of migrainous aura in the past. I find it very difficult to present cases with this diagnosis, because once you put it all out there, then people pay attention. Whereas if they had to get the information themselves, they don't. And the take-home message from me in this case is actually the other way around. My take-home message is you always have to think of GCA first. Then you can take a little bit of extra time to figure out that it is actually ipsilateral carotid disease and do secondary prevention. But in my mind, anybody aged 50 years and older who has the most benign systemic symptoms and an episode of transient vision loss has to have GCA ruled out,[33] at least with systemic markers first.

DR. MILLER: I agree with you.

DR. CALABRESE: I'd like to add that this is an opportunity now to drill into the history in a more refined way. TMJ disease means nothing to me. I want to know whether this is jaw claudication, something that patients don't always proffer. I'd like them to describe TMJ pain. Is it pain in the jaw or the jaw area that comes on rapidly with chewing? Some people describe TMJ pain mistakenly as actual pain in their mouth, as opposed to pain in their jaw. So I would drill into that. Secondly, I'd like to hear more about the headaches because those associated with GCA are nondescript, lasting the past 2 months. I would like to know more about the 10-lb weight loss, such as any evidence of anemia, chronic disease, new fatigue, joint pain, etc. Those are just some of the nuances that I would be thinking about.

DR. MILLER: Agreed.

CASE 2

An Indian woman, age 80, developed horizontal, binocular double vision 3 weeks ago. She endorses pain in the right eye radiating to the right temple and neck that coincided with the double vision. She has a foreign body sensation in the right eye. There is no blurring of the vision with either eye closed. There is no ptosis. The double vision initially lasted seconds at a time occurring a few times a day and became constant 1 week ago. She was placed on 40 mg prednisone 1 day ago with improvement in her headache.

PAST MEDICAL HISTORY

- Polymyalgia rheumatica 8 to 10 years
- Hysterectomy at age 35
- Cataract extraction OU 1 year ago

MEDICATIONS

- Prednisone 40 mg x 1 day
- Calcium
- Vitamin D
- Vitamin B_{12}
- Multivitamin

FAMILY HISTORY

- Father: lung cancer
- Mother: liver cancer

SOCIAL HISTORY

- Homemaker
- Never smoked
- Consumes 1 to 2 glasses of wine weekly

REVIEW OF SYSTEMS

- Arthritis in the shoulders and hips
- Depression

EXAMINATION

Visual acuity	20/25 OD 20/40 OS
Pupils	Equal, normal
Color vision	Normal OU
Intraocular pressure	17 mm Hg OU
External	Mild ptosis OU, no orbicularis weakness, normal facial sensation
Slit lamp	Intraocular lens OU
Fundus examination	Elevation of both optic nerves, + spontaneous venous pulsations (SVP), anomalous vessels on disc
Motility	50% abduction deficit OD
Alignment	Esotropia worse in right gaze and better in left gaze
Neurologic	Normal hearing to finger rub, no focal weakness or numbness

DR. NEWMAN: In this setting, of course she has GCA. But who would have thought to ask the right questions? And then, just like C. Miller Fisher, MD, would have said, "If you have asked enough questions, who would have figured out which ones to throw away that don't matter?" Because, that is really what is needed. Any elderly person who has transient double vision, if they receive a delayed diagnosis of myasthenia, they are okay. A delayed diagnosis of GCA or vertebrobasilar disease is not okay. Even though they are much less common, physicians need to push the GCA envelope when a patient has these symptoms.

DR. MILLER: This brings up the issue of patients with PMR for an extended time, subsequently developing GCA. This patient had PMR for 8 to 10 years and now has GCA. Dr. Calabrese, how often do you see that?

DR. CALABRESE: That's one of the "devil in the details" scenarios. PMR diagnosis in the community is often a broader presentation of symptoms than the classification criteria. These diseases are far more chronic than we admit. A beautiful Mayo Clinic study from last year did serial biopsies on patients with GCA.[62] After 1 year, 40% of patients in clinical remission still had active arteritis. We have known this anecdotally for years. Thus, these are chronic illnesses. We know that the large-vessel involvement of GCA, aneurysms in particular, develop after years. I would love to get a more detailed history of that patient and know that she has an appropriate response to steroids. This case is very curious and interesting.

DR. MILLER: If you have a patient in whom you're comfortable with the diagnosis of PMR, and she or he is on 5 mg/day of prednisone, are you still concerned that she or he may transition to GCA?

DR. CALABRESE: Yes, although I can't say that it is common. Exacerbations over many, many years with PMR are not uncommon. Late-onset vision loss is rare, and I don't remember any case in these decades-long follow-ups. PMR is a chronic illness often.

DR. LEE: Let's move on to look at the data in these cases.

CASE DATA

CASE 1

The patient endorsed jaw fatigue with prolonged chewing that improved over several minutes with rest. He had been eating softer foods to accommodate this pain. Examination showed mild tenderness of both temples with a reduced pulse on the right side. A fluorescein angiogram was not performed.

DATA:

- ESR: 35 mm/hour
- CRP: 8.6 mg/L (normal < 8 mg/L)
- Carotid ultrasound: < 50% stenosis
- Transthoracic echo and EKG: normal
- MRI brain: White matter lesions consistent with small vessel ischemic disease
- Temporal artery biopsy: Inflammation of the vessel walls consistent with GCA

CASE 2

The patient denies jaw claudication, scalp tenderness, or weight loss. The temporal artery pulses were normal and not tender. A fluorescein angiogram did not show late leakage from either optic nerve or delayed choroidal filling.

DATA:

- ESR: 17 mm/hour
- CRP: 20 mg/L (normal < 8)
- MRI brain: White matter lesions consistent with small vessel ischemic disease, left frontal bone abnormality, cerebral atrophy consistent with age
- Temporal artery biopsy: Segmental transmural scarring with loss of the internal elastic lamina consistent with healed arteritis

DR. CALABRESE: Case 1 is one of those really tough calls. ESR of 35 mm/hr is no big deal. But CRP at 8.6 mg/L is an elevated CRP to me.

DR. MILLER: The ESR by "Miller's" method is 1 point more, 1 mm/hr more than normal. It should be 34 mm/hr, and it is 35 mm/hr.

DR. CALABRESE: Exactly. All that we are saying is that if acute phase reactants are rock-solid normal, it has negative predictive values, as they are elevated in 99% of patients. This case does not have that. So, the game is still afoot.

DR. MILLER: Exactly.

DR. NEWMAN: Every year we do a course at the American Academy of Ophthalmology. One year we presented a series of cases that all ended up with GCA, and none of us would have had that pop in our head. Physicians have to think about GCA all the time and eliminate the diagnosis. If not, you are going to miss it.

DR. MILLER: Dr. Calabrese advised that we take a more detailed history. When the patient has TMJ, but then you hear the actual symptoms, it is not TMJ.

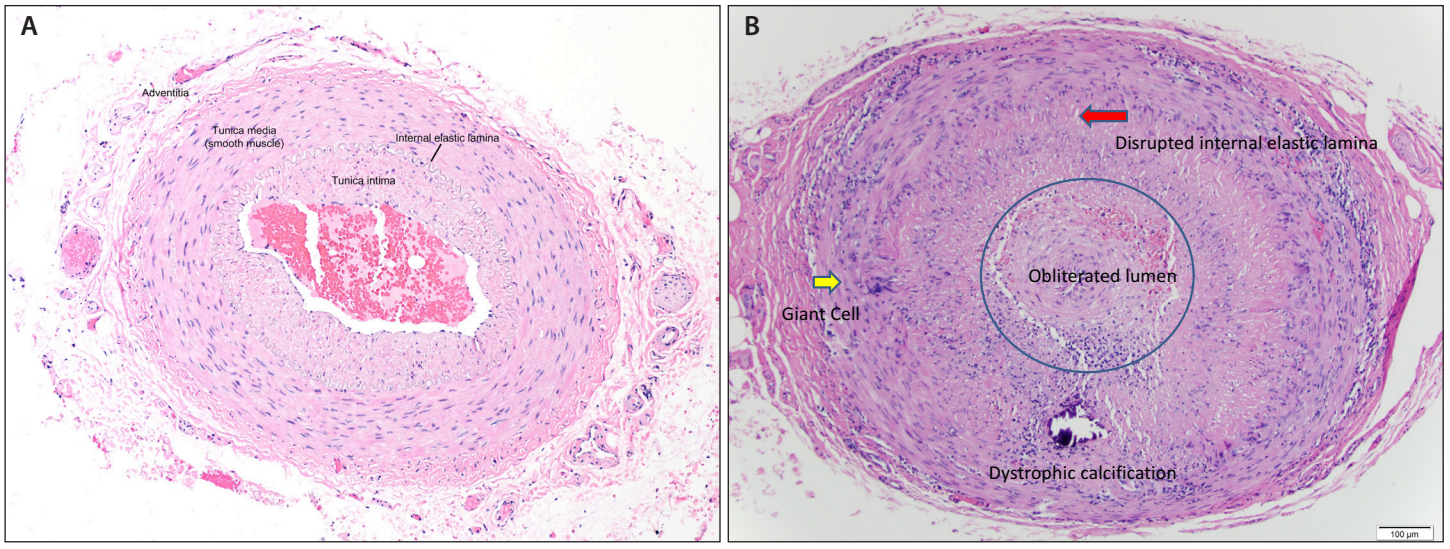

Figure 1. Hematoxylin and eosin stained cross section of normal and abnormal temporal arteries. Normal temporal artery showing the layers of the artery wall including an intact internal elastic lamina (A). Abnormal temporal artery shows arterial wall inflammation including giant cell arteritis (GCA) (B). Image also shows a disruption of the internal elastic lamina and a complete obliteration of the normal vessel lumen. Image courtesy of John D. Cameron, MD, MBA, University of Minnesota, Minneapolis. (The image shown demonstrates features similar to those found in case 1 but is not directly from case 1.)

DR. CALABRESE: Yes, CRP in somebody that had TMJ syndrome for 30 years is not much concern. That same CRP level in somebody who now describes classic jaw claudication, you immediately think GCA.

DR. LEE: The TAB of case 1 showed typical inflammation for GCA, such as seen in Figure 1. case 2 has that segmental transmural scarring with loss of internal elastic lamina. Similar pathology is shown in Figure 2.

DR. MILLER: And a very elevated CRP.

DR. CALABRESE: That is a really significant discord there. With diplopia, where would you go with that?

DR. LEE: That's a good question, whether you treat patients for GCA or you don't treat them for GCA.

DR. CALABRESE: If it's a loss of the internal elastic lamina with not one scintilla of inflammation, I think there are 3 choices: 1) empiric therapy (steroid); 2) assuming that this temporal artery has been anteriorly sectioned and handled properly, do a contralateral temporal artery biopsy; but I probably would do 3) large-vessel imaging as my next study.

DR. MILLER: I agree with large-vessel imaging. If not imaging, my default would be to treat the patient. Although she is 80, she is medically well. No major contraindications to steroids. She does have pain in the right eye radiating to the right temple and neck. I would have treated her, and I see that when she was placed on the prednisone she improved. Whether that means she had GCA, I don't know. And I agree. This is one where I probably would biopsy the other side. That's why she needs to be treated with TCZ after a short period of steroids.

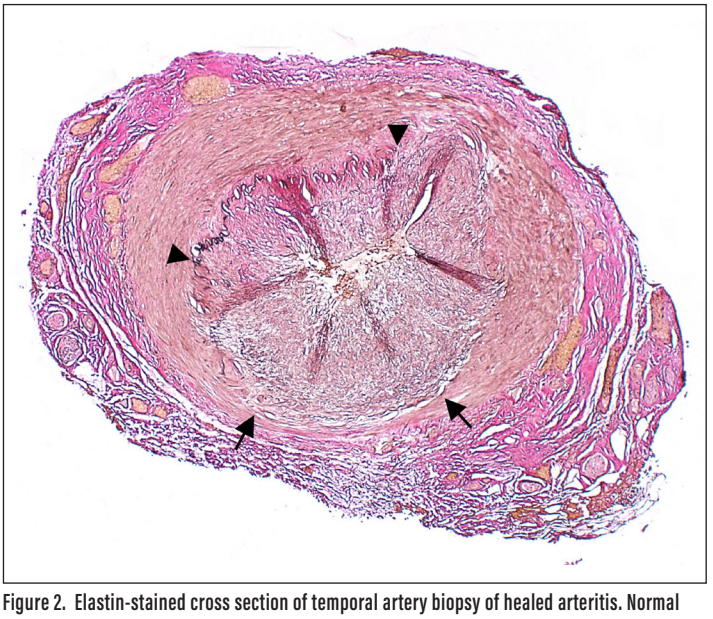

Figure 2. Elastin-stained cross section of temporal artery biopsy of healed arteritis. Normal internal elastic lamina is seen between the arrowheads. Absence of the lamina is seen between the arrows. Image courtesy of Amanda C. Maltry, MD, University of Minnesota, Minneapolis. (The image shown demonstrates features similar to those found in case 2 but is not directly from case 2.)

DR. NEWMAN: I would probably biopsy the other side, as well, because she is going to be your poster child for steroid complications.

CASE CONCLUSION

CASE 1

The patient was started on IV solumedrol 1 g/day for 3 days followed by prednisone 80 mg/day (80 kg man). The prednisone was tapered weekly until the patient reached a dose of 40 mg/day by 1 month. The prednisone was then tapered over 2 years without recurrence.

CASE 2

The patient was maintained on prednisone 40 mg/day (55 kg woman) and tapered slowly over 1 year to her maintenance dose of 5 mg/day for her PMR.

DR. LEE: In summary, GCA affects people of all races and people who are older than age 50. Patients' presentations vary widely, and its diagnosis and treatment are urgent to avoid visual manifestations and, less frequently, cerebrovascular events. Physicians should consider a GCA diagnosis in patients with fever or inflammatory disease of unknown origin, recent headaches, fatigue, malaise, jaw claudication that may have been misdiagnosed as TMJ, and/or visual symptoms and findings such as transient or persistent diplopia, transient monocular vision loss, permanent vision loss, choroidal ischemia, AION, and less common PION.

We recommend a TAB on the affected side to confirm the diagnosis and possibly a TAB of the second side if the first side appears negative and suspicions are high. If the patient has any visual or cerebrovascular manifestations, we recommend rapid (same day) initiation of steroids, such as high-dose IV steroids for 3 days and continuation on oral steroids thereafter. Depending on the patient, most of us consider a low-dose aspirin adjunctive therapy for 2 weeks.

Steroids remain the initial therapy in all patients with GCA, and in many cases, steroid tapering can begin 2 to 4 weeks after initiation. Patients may be on steroids for 3 years or more with traditional steroid-tapering regimens, making them at high risk for developing steroid-associated complications and declines in quality of life. Most of us have begun advocating for the recent FDA-approved TCZ in an adjuvant manner to patients with GCA. TCZ improves the rapidity of steroid-tapering regimens and reduces the total prednisone dose required. The treatment of each patient with GCA may need adjustment due to unexpected flares and/or steroid-associated complications.

Thank you, everyone, for participating. ■

1. Chandran AK, Udayakumar PD, Crowson CS, Warrington KJ, Matteson EL. The incidence of giant cell arteritis in Olmsted County, Minnesota, over a 60-year period 1950-2009. *Scand J Rheumatol*. 2015;44(3):215-218.
2. Muratore F, Kermani TA, Crowson CS, et al. Large-vessel giant cell arteritis: a cohort study. *Rheumatology (Oxford)*. 2015;54(3):463-470.
3. Garrity ST, Pistilli M, Vaphiades MS, et al. Ophthalmic presentation of giant cell arteritis in African-Americans. *Eye (Lond)*. 2017;31(1):113-118.
4. Ji J, Dimitrijevic I, Sundquist J, Sundquist K, Zoller B. Risk of ocular manifestations in patients with giant cell arteritis: a nationwide study in Sweden. *Scand J Rheumatol*. 2017:1-6.
5. Soriano A, Muratore F, Pipitone N, Boiardi L, Cimino L, Salvarani C. Visual loss and other cranial ischaemic complications in giant cell arteritis. *Nat Rev Rheumatol*. 2017;13(8):476-484.
6. Murchison AP, Gilbert ME, Bilyk JR, et al. Validity of the American College of Rheumatology criteria for the diagnosis of giant cell arteritis. *Am J Ophthalmol*. 2012;154(4):722-729.
7. Melson MR, Weyand CM, Newman NJ, Biousse V. The diagnosis of giant cell arteritis. *Rev Neurol Dis*. 2007;4(3):128-142.
8. Dejaco C, Duftner C, Buttgereit F, Matteson EL, Dasgupta B. The spectrum of giant cell arteritis and polymyalgia rheumatica: revisiting the concept of the disease. *Rheumatology (Oxford)*. 2017;56(4):506-515.
9. Watanabe R, Goronzy JJ, Berry G, Liao YJ, Weyand CM. Giant cell arteritis: From pathogenesis to therapeutic management. *Curr Treatm Opt Rheumatol*. 2016;2(2):126-137.
10. Watanabe R, Hosgur E, Zhang H, et al. Pro-inflammatory and anti-inflammatory T cells in giant cell arteritis. *Joint Bone Spine*. 2017;84(4):421-426.
11. Terrier B, Geri G, Chaara W, et al. Interleukin-21 modulates Th1 and Th17 responses in giant cell arteritis. *Arthritis Rheum*. 2012;64(6):2001-2011.
12. Gilden D, Nagel M. Varicella Zoster virus in temporal arteries of patients with giant cell arteritis. *J Infect Dis*. 2015;212 Suppl 1:S37-39.
13. Gilden D, White T, Khmeleva N, Katz BJ, Nagel MA. Blinded search for varicella zoster virus in giant cell arteritis (GCA)-positive and GCA-negative temporal arteries. *J Neurol Sci*. 2016;364:141-143.
14. Procop GW, Eng C, Clifford A, et al. Varicella zoster virus and large vessel vasculitis, the absence of an association. *Pathog Immun*. 2017;2(2):228-238.
15. Muratore F, Croci S, Tamagnini I, et al. No detection of varicella-zoster virus in temporal arteries of patients with giant cell arteritis. *Semin Arthritis Rheum*. 2017.
16. Rondaan C, van der Geest KSM, Eelsing E, et al. Decreased Immunity to Varicella zoster virus in giant cell arteritis. *Front Immunol*. 2017;8:1377.
17. Alvarez-Lafuente R, Fernandez-Gutierrez B, Jover JA, et al. Human parvovirus B19, varicella zoster virus, and human herpes virus 6 in temporal artery biopsy specimens of patients with giant cell arteritis: analysis with quantitative real time polymerase chain reaction. *Ann Rheum Dis*. 2005;64(5):780-782.
18. Rhee RL, Grayson PC, Merkel PA, Tomasson G. Infections and the risk of incident giant cell arteritis: a population-based, case-control study. *Ann Rheum Dis*. 2017;76(6):1031-1035.
19. Miller A, Green M, Robinson D. Simple rule for calculating normal erythrocyte sedimentation rate. *Br Med J (Clin Res Ed)*. 1983;286(6361):266.
20. Parikh M, Miller NR, Lee AG, et al. Prevalence of a normal C-reactive protein with an elevated erythrocyte sedimentation rate in biopsy-proven giant cell arteritis. *Ophthalmology*. 2006;113(10):1842-1845.
21. Kermani TA, Schmidt J, Crowson CS, et al. Utility of erythrocyte sedimentation rate and C-reactive protein for the diagnosis of giant cell arteritis. *Semin Arthritis Rheum*. 2012;41(6):866-871.
22. Monti S, Floris A, Ponte C, et al. The use of ultrasound to assess giant cell arteritis: review of the current evidence and practical guide for the rheumatologist. *Rheumatology (Oxford)*. 2018;57(2):227-235.
23. Monti S, Floris A, Ponte CB, et al. The proposed role of ultrasound in the management of giant cell arteritis in routine clinical practice. *Rheumatology (Oxford)*. 2018;57(1):112-119.
24. Schafer VS, Juche A, Ramiro S, Krause A, Schmidt WA. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. *Rheumatology (Oxford)*. 2017.
25. Daily B, Dassow P, Haynes J, Nashelsky J. Giant cell arteritis: Biopsy after corticosteroid initiation. *Am Fam Physician*. 2017;95(2):116-117.
26. Prieto-Gonzalez S, Arguis P, Garcia-Martinez A, et al. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. *Ann Rheum Dis*. 2012;71(7):1170-1176.
27. Germano G, Muratore F, Cimino L, et al. Is colour duplex sonography-guided temporal artery biopsy useful in the diagnosis of giant cell arteritis? A randomized study. *Rheumatology (Oxford)*. 2015;54(3):400-404.
28. Durling B, Toren A, Patel V, Gilberg S, Weis E, Jordan D. Incidence of discordant temporal artery biopsy in the diagnosis of giant cell arteritis. *Can J Ophthalmol*. 2014;49(2):157-161.
29. Breuer GS, Nesher G, Nesher R. Rate of discordant findings in bilateral temporal artery biopsy to diagnose giant cell arteritis. *J Rheumatol*. 2009;36(4):794-796.
30. Pless M, Rizzo JF, 3rd, Lamkin JC, Lessell S. Concordance of bilateral temporal artery biopsy in giant cell arteritis. *J Neuroophthalmol*. 2000;20(3):216-218.
31. Danesh-Meyer HV, Savino PJ, Eagle RC, Jr., Kubis KC, Sergott RC. Low diagnostic yield with second biopsies in suspected giant cell arteritis. *J Neuroophthalmol*. 2000;20(3):213-215.
32. Boyev LR, Miller NR, Green WR. Efficacy of unilateral versus bilateral temporal artery biopsies for the diagnosis of giant cell arteritis. *Am J Ophthalmol*. 1999;128(2):211-215.
33. Chen JJ, Leavitt JA, Fang C, Crowson CS, Matteson EL, Warrington KJ. Evaluating the incidence of arteritic ischemic optic neuropathy and other causes of vision loss from giant cell arteritis. *Ophthalmology*. 2016;123(9):1999-2003.
34. Kaptanis S, Perera JK, Halkias C, Caton N, Alarcon L, Vig S. Temporal artery biopsy size does not matter. *Vascular*. 2014;22(6):406-410.
35. Au C, Sharma N, McCluskey P, Ghabrial R. Length of temporal artery biopsies. *Clin Experiment Ophthalmol*. 2016.
36. Oh LJ, Wong E, Gill AJ, McCluskey P, Smith JE. Value of temporal artery biopsy length in diagnosing giant cell arteritis. *ANZ J Surg*. 2016.
37. McDonnell PJ, Moore GW, Miller NR, Hutchins GM, Green WR. Temporal arteritis. A clinicopathologic study. *Ophthalmology*. 1986;93(4):518-530.
38. Restuccia G, Boiardi L, Cavazza A, et al. Long-term remission in biopsy proven giant cell arteritis: A retrospective cohort study. *J Autoimmun*. 2017;77:39-44.
39. Lo Gullo A, Koster MJ, Crowson CS, et al. Venous thromboembolism and cerebrovascular events in patients with giant cell arteritis: A population-based retrospective cohort study. *PLoS One*. 2016;11(2):e0149579.
40. de Boysson H, Liozon E, Lariviere D, et al. Giant cell arteritis-related stroke: A retrospective multicenter case-control study. *J Rheumatol*. 2017;44(3):297-303.
41. Scheurer RA, Harrison AR, Lee MS. Treatment of vision loss in giant cell arteritis. *Curr Treat Options Neurol*.

2012;14(1):84-92.
42. Liu GT, Glaser JS, Schatz NJ, Smith JL. Visual morbidity in giant cell arteritis. Clinical characteristics and prognosis for vision. *Ophthalmology*. 1994;101(11):1779-1785.
43. Chan CC, Paine M, O'Day J. Steroid management in giant cell arteritis. *Br J Ophthalmol*. 2001;85(9):1061-1064.
44. Dasgupta B, Borg FA, Hassan N, et al. BSR and BHPR guidelines for the management of giant cell arteritis. *Rheumatology (Oxford)*. 2010;49(8):1594-1597.
45. Hayreh SS, Biousse V. Treatment of acute visual loss in giant cell arteritis: should we prescribe high-dose intravenous steroids or just oral steroids? *J Neuroophthalmol*. 2012;32(3):278-287.
46. Fraser JA, Weyand CM, Newman NJ, Biousse V. The treatment of giant cell arteritis. *Rev Neurol Dis*. 2008;5(3):140-152.
47. Buono LM, Foroozan R, de Virgiliis M, Savino PJ. Heparin therapy in giant cell arteritis. *Br J Ophthalmol*. 2004;88(2):298-301.
48. Lee MS, Smith SD, Galor A, Hoffman GS. Antiplatelet and anticoagulant therapy in patients with giant cell arteritis. *Arthritis Rheum*. 2006;54(10):3306-3309.
49. Chandran A, Udayakumar PD, Kermani TA, Warrington KJ, Crowson CS, Matteson EL. Glucocorticoid usage in giant cell arteritis over six decades (1950 to 2009). *Clin Exp Rheumatol*. 2015;33(2 Suppl 89):S-98-102.
50. Labarca C, Koster MJ, Crowson CS, et al. Predictors of relapse and treatment outcomes in biopsy-proven giant cell arteritis: a retrospective cohort study. *Rheumatology*. 2015.
51. Alba MA, Garcia-Martinez A, Prieto-Gonzalez S, et al. Relapses in patients with giant cell arteritis: prevalence, characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients. *Medicine (Baltimore)*. 2014;93(5):194-201.
52. Kermani TA, Warrington KJ, Cuthbertson D, et al. Disease relapses among patients with giant cell arteritis: A prospective, longitudinal cohort study. *J Rheumatol*. 2015;42(7):1213-1217.
53. Hoffman GS, Cid MC, Hellmann DB, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum*. 2002;46(5):1309-1318.
54. Mahr AD, Jover JA, Spiera RF, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. *Arthritis Rheum*. 2007;56(8):2789-2797.
55. Leon L, Rodriguez-Rodriguez L, Freites D, et al. Long-term continuation of methotrexate therapy in giant cell arteritis patients in clinical practice. *Clin Exp Rheumatol*. 2017;35 Suppl 103(1):165-170.
56. Yates M, Loke YK, Watts RA, MacGregor AJ. Prednisolone combined with adjunctive immunosuppression is not superior to prednisolone alone in terms of efficacy and safety in giant cell arteritis: meta-analysis. *Clin Rheumatol*. 2014;33(2):227-236.
57. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of Tocilizumab in giant-cell arteritis. *N Engl J Med*. 2017;377(4):317-328.
58. Villiger PM, Adler S, Kuchen S, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet*. 2016;387(10031):1921-1927.
59. Xie F, Yun H, Bernatsky S, Curtis JR. Brief Report: Risk of gastrointestinal perforation among rheumatoid arthritis patients receiving tofacitinib, Tocilizumab, or other biologic treatments. *Arthritis Rheumatol*. 2016;68(11):2612-2617.
60. Lally L, Forbess L, Hatzis C, Spiera R. Brief Report: A prospective open-label phase IIa trial of tocilizumab in the treatment of polymyalgia rheumatica. *Arthritis Rheumatol*. 2016;68(10):2550-2554.
61. Devauchelle-Pensec V, Berthelot JM, Cornec D, et al. Efficacy of first-line tocilizumab therapy in early polymyalgia rheumatica: a prospective longitudinal study. *Ann Rheum Dis*. 2016;75(8):1506-1510.
62. Maleszewski JJ, Younge BR, Fritzlen JT, et al. Clinical and pathological evolution of giant cell arteritis: a prospective study of follow-up temporal artery biopsies in 40 treated patients. *Mod Pathol*. 2017;30(6):788-796.

DIAGNOSING AND TREATING GIANT CELL ARTERITIS WITH VISUAL AND NEUROLOGIC IMPAIRMENTS

Release Date: May 2018
Expiration Date: May 2019

INSTRUCTIONS FOR CME CREDIT

To receive *AMA PRA Category 1 Credit™*, you must complete the attached Posttest/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC, 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087, Fax: (215) 933-3950. To answer these questions online and receive real-time results, please visit evolvemeded.com and click on "Online Courses." If you are experiencing problems with the online test, please email us at support@evolvemeded.com. Certificates are issued electronically; please be certain to provide your email address below.

Please type or print clearly, or we will be unable to issue your certificate.

Name _____ ❑ MD participant ❑ non-MD participant

Phone (required) _____ ❑ Email (required) _____

Address _____

City _____ State _____ Zip _____

License Number _____

DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ >20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this activity)
___ 0
___ 1-5
___ 6-10
___ 11-15
___ 15-20
___ 20+

Region
___ Northeast
___ Northwest
___ Mid-West
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

Training of Fellows ___ Yes ___ No

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Recall patient risk factors and symptoms of giant cell arteritis (GCA) based on relevant classification and diagnostic criteria to confidently add GCA as a differential diagnosis.	_____	_____	_____
Distinguish among the visual abnormalities and ischemic events associated with GCA versus other causes.	_____	_____	_____
Formulate treatment options for patients with recently diagnosed GCA, including GC-sparing regimens and second-line therapy.	_____	_____	_____
Evaluate treatment options for patients with relapsing GCA and glucocorticoid-resistant GCA to determine if management is needed long term.	_____	_____	_____
Outline the underlying inflammatory processes involved in GCA.	_____	_____	_____
Outline the evidence for targeted therapy approved by the Food and Drug Administration (FDA), along with emerging therapies for the treatment of patients with GCA, including use as second-line therapy.	_____	_____	_____

POSTTEST QUESTIONS

1. **WHICH DEMOGRAPHIC FACTOR IS NOT ASSOCIATED WITH A DIAGNOSIS OF GIANT CELL ARTERITIS (GCA)?**
   a. Northern European or Scandinavian origin
   b. Age 50 years or older
   c. Female sex
   d. Age 40 years or older

2. **WHICH SYSTEMIC SYMPTOM(S) MAY BE ASSOCIATED WITH GCA?**
   a. New fatigue
   b. Fever of unknown origin
   c. Weight loss
   d. Anemia of chronic disease
   e. All of the above

3. **WHAT DOES NOT CAUSE VISUAL LOSS IN PEOPLE WITH GCA?**
   a. Anterior ischemic optic neuropathy
   b. Central retinal artery occlusion
   c. Branch retinal artery occlusion
   d. Posterior ischemic optic neuropathy
   e. Choroidal ischemia

4. **WHAT ARE RISK FACTORS FOR STROKES IN PATIENTS WITH GCA?**
   a. Very high levels of inflammatory markers such as high ESR and high CRP
   b. Diabetes, hypertension, and cardiovascular risk factors
   c. A previous ischemic event in a patient with GCA
   d. Elevated, but not extremely elevated, levels of inflammatory markers
   e. a, b, & c
   f. b, c, & d

5. **WHAT IS THE MOST IMPORTANT IMMEDIATE MANAGEMENT WHEN TREATING PATIENTS WITH TRANSIENT MONOCULAR VISION LOSS AND A SUSPICION OF GCA?**
   a. Confirmed diagnosis with positive temporal artery biopsy
   b. Oral steroids, 40 mg/day to 60 mg/day
   c. Rapid treatment, beginning on the same day as the visit
   d. Confirmed abnormal ESR and/or abnormal CRP

6. **WHICH OF THE FOLLOWING ARE COMMON SCENARIOS THAT SLOW DOWN THE RATE OF TAPERING OF THE STEROID DOSAGE?**
   a. Patients have comorbidities, such as osteopenia, osteoporosis, diabetes, or glaucoma
   b. Patients have developed a headache or new fatigue during the steroid-tapering process
   c. Patients have an improved quality of life, according to the SF-36
   d. Patients with GCA develop a serious infection

7. **WHICH AGENT IS APPROVED BY THE FOOD AND DRUG ADMINISTRATION FOR TREATING GCA IN A STEROID-SPARING REGIMEN?**
   a. Tocilizumab (TCZ)
   b. Methotrexate
   c. Infliximab
   d. Azathioprine

8. **WHEN TCZ IS USED TO TREAT GCA IN A STEROID-SPARING REGIMEN, WHAT EFFECT DOES TCZ TREATMENT HAVE ON QUALITY OF LIFE?**
   a. Higher quality of life, as measured by SF-36
   b. Lower quality of life, as measured by SF-36
   c. Higher quality of life than age- and sex-matched peers without GCA
   d. Lower quality of life than age- and sex-matched peers without GCA
   e. a & c
   f. b & d

9. **HOW MUCH DID TCZ TREATMENT INCREASE THE RATE OF SUSTAINED PREDNISONE-FREE REMISSION AT WEEK 52 IN THE PHASE 3 TRIAL?**
   a. Twofold higher rate of sustained prednisone-free remission at week 52 in the phase 3 trial
   b. Threefold higher rate of sustained prednisone-free remission at week 52 in the phase 3 trial
   c. Fourfold higher rate of sustained prednisone-free remission at week 52 in the phase 3 trial
   d. Fivefold higher rate of sustained prednisone-free remission at week 52 in the phase 3 trial

10. **WHICH OF THE FOLLOWING CYTOKINES ARE NOT INVOLVED IN THE PATHOGENESIS OF GCA?**
    a. IL-4
    b. IL-6
    c. IL-17
    d. IL-21

ACTIVITY EVALUATION/SATISFACTION MEASURES

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME).

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

This activity improved my competence in managing patients with this disease/condition/symptom _____ Yes _____ No

I plan to make changes to my practice based on this activity _____ Yes _____ No

Please identify any barriers to change (check all that apply):

_____ Cost

_____ Lack of administrative support

_____ Lack of time to assess/counsel patients

_____ Reimbursement/insurance issues

_____ Patient compliance issues

_____ Lack of consensus or professional guidelines

_____ Lack of experience

_____ Lack of opportunity (patients)

_____ Lack of resources (equipment)

_____ No barriers

_____ Other. Please specify: _____

The design of the program was effective for the content conveyed. ___ Yes ___ No

The content supported the identified learning objectives. ___ Yes ___ No

The content was free of commercial bias. ___ Yes ___ No

The content was relative to your practice. ___ Yes ___ No

The faculty was effective. ___ Yes ___ No

You were satisfied overall with the activity. ___ Yes ___ No

Would you recommend this program to your colleagues? ___ Yes ___ No

Please check the Core Competencies (as defined by the ACCME) that were enhanced through your participation in this activity:

_____ Patient Care

_____ Practice-Based Learning and Improvement

_____ Professionalism

_____ Medical Knowledge

_____ Interpersonal and Communication Skills

_____ System-Based Practice

Additional comments:

_____

_____ I certify that I have participated in this entire activity.

This information will help us evaluate this CME activity. May we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

_____