

Clinical findings and management of giant cell arteritis

Abstract

Purpose: Giant cell arteritis (GCA) is a systemic vasculitis that tends to have a predilection for involving the medium and large size vessels throughout the body, especially branches of the carotid arteries. Caucasian women over the age of 50 are those most likely to be affected by GCA, with incidence of developing GCA increasing with each decade of life. Also, those of north-western European descent tend to have a higher rate of developing this condition, and based on current research there appears to be a genetic component for increased rate of developing GCA. GCA can affect the short posterior ciliary arteries, which can cause edema secondary to the occlusion of the artery, and effectively shut off input from the optic nerve, causing the patient to lose vision and develop profound vision loss.

Case report: This case report is a review of the typical management of a patient with GCA and discusses clinical findings and treatment.

Conclusion: The natural course of GCA without treatment is usually permanent vision loss that tends to be profound, resulting in the patient becoming profoundly visually impaired in one eye. The goal of treating GCA is to prevent vision loss in the other eye, since GCA is a systemic inflammation. It is important for clinicians to be able to appreciate and realize the clinical signs and symptoms of this condition, understand the prognosis of the disease, and to be able to appropriately apply treatment and intervention.

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Abbreviations: GCA, giant cell arteritis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NAION, non-arteritic anterior ischemic optic neuropathy

Introduction

Giant cell arteritis, also known as temporal arteritis or Horton's arteritis is a disease that tends to affect medium and large size arteries throughout the body. This tends to be a granulomatous inflammation which can cause a large amount of edema and tends to have more generalized inflammation than a non-granulomatous inflammation due to the high amount of complement factors that giant cells tend to attract.¹⁻⁶ This disease tends to present in the sixth decade of life, predominantly in Caucasian women of northern European descent.⁷⁻¹¹ There is believed to be a correlation between patients who have polymyalgia rheumatica and those who develop GCA, although there is no direct test to determine patients who have polymyalgia rheumatica, thus making it difficult to "pre-treat" those at risk for GCA.¹²⁻¹⁴ Additional research on this condition has begun and there is a generalized trend showing that there may be a genetic component involved in this condition as well. The genetic component is believed to be associated with HLA-DR4 haplotype and with those that have changes in the ICAM-1 gene (which can promote more inflammatory processes and more adhesions).

There are two types of general complications that can occur from GCA, those that are due to tissue ischemia and those that are actually due to the inflammatory component.¹⁻¹⁷ For the GCA that affects the eyes, headaches that are debilitating and are of new onset tend to be one of the most commonly reported symptoms, especially if their location is temporal, which can indicate temporal arteritis of the temporal artery. Additional symptoms that may be reported by patients

are pain while combing or brushing their hair, pain when rubbing their temples, pain or fatigue after talking or chewing for a great deal of time. If a patient is not only affected by the ocular component of GCA, but also has systemic components, they may report excessive fatigue when trying to change body positions (i.e. going from walking to sitting down, or laying down to sitting up), fever, cold sweats, and/or unexplainable weight loss.

Specific visual symptoms that clinicians need to be aware of are transient or permanent visual distortion or loss of vision in one or both eyes, double vision, occasionally hallucinations, and ocular pain. Permanent vision loss tends to result in patients diagnosed with GCA, especially if it is left untreated; this vision loss can be unilateral or bilateral depending on when treatment is initiated. The vision loss is either related to the actual ischemia of the optic nerve, retinal/choroidal ischemia, or occasionally occipital lobe infarction. If GCA is suspected in a patient, same day erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) blood tests should be performed and high dose corticosteroids should be prescribed for the patient, even before a temporal artery biopsy is performed. The idea behind the high dose corticosteroids is to reduce the systemic inflammation and essentially "protect" the eye that still has vision remaining.^{1-16,18-22}

Case report

Patient JA, age 61, presented to clinic for a comprehensive eye examination. The patient complained about pain surrounding the left orbit, that has been going on for the past few months. He also reported that there was some pain around his temporal artery when he was combing his hair. This tenderness could not be elicited in office when the area was palpated. Mr JA also reported occasional jaw fatigue when he was chewing his steak dinner the night before.

He also reported that subjectively his eye was starting to feel like his right one did before he had a non-arteritic anterior ischemic optic neuropathy (NAION). The patient's last eye examination was three months prior with significant finding of prior NAION from July 2011 OD and no other pathology noted. The patient's past ocular history contains nothing of significance other than prior NAION OD. The patient had positive medical history for type 2 diabetes mellitus that did not require insulin to manage, hypertension, high cholesterol, carotid artery stenosis, and chronic kidney disease.

His best corrected visual acuity was CF @3 ft OD with no improvement on refraction or with pinhole, 20/20- OS. Pupil testing revealed slight reaction OU, however it was difficult to assess RAPD status secondary to patient's 1 mm pupil size and the compounding factors of his longstanding diabetes and hypertension. Confrontation fields were constricted 360 OD and full to finger count OS. Anterior segment evaluation was normal. Dilated posterior segment evaluation revealed, the optic nerve in the right eye had a cup to disc ratio of 0.20 round and had pallor 360 degrees and the optic nerve in the left eye had a cup to disc ratio of 0.25 round with good color and distinct margins, no edema was noted anywhere in the nerve. There were no other significant finding noted in the posterior poles, no diabetic retinopathy, or macular edema. There were also no holes, tears, or detachments in the periphery bilaterally.

Additional testing that was performed that day was a complete blood count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). These tests were ordered same day in order to rule out giant cell arteritis. His CRP came back as 0.72, which was outside of the lab's normal range of 0.0-0.50. His ESR came back as 36, which was age appropriate for this patient, but outside of the lab's normal range of 0-15. His ESR has been as high as 58 in the past (2000). After receiving the lab results a phone call was placed to a neuro-ophthalmologist for phone consultation on whether steroids should be started, since the patient was experiencing some symptoms of GCA, but there were no signs, and the lab results did not really support that diagnosis. The neuro-ophthalmologist reported that he was not really concerned about the patient having giant cell arteritis at the time because of lack of signs and laboratory support. A referral was placed for the patient to have further evaluation with the neuro-ophthalmologist.

Based on the history, Mr. JA most likely was experiencing either an NAION or an AION. He did not fit the profile for having optic neuritis and he had no ocular signs that would be associated with a compressive lesion. Migraine was a possibility for the patient as there was unilateral pain for the patient, but he didn't complain of a headache so much as the tenderness located around the temporal artery. In order to differentiate between an NAION and GCA, a stat ESR/CRP panel is obtained, along with considering a temporal artery biopsy. In addition, a fluorescein angiogram can be performed which would show choroidal nonperfusion in GCA.

The patient presented for his follow-up to the neuro-ophthalmologist, reporting the same chief complaint with one additional symptom, he now had a headache that was persistent. Mr. JA, upon further questioning, also revealed that he has been losing weight without trying and he overall has been very lethargic. Mr. JA presented with best corrected visual acuity of CF @ 3 feet OD and 20/20 OS. His confrontation visual fields still showed severe constriction 360 degrees OD and he was full to finger count OS. Pupillary testing revealed a relative afferent pupillary defect OD.

His anterior segment slit lamp examination revealed no significant findings. His posterior pole examination revealed no changes from the previous visit. Additional testing that was ordered for that patient immediately was an ESR and CRP. At this visit the ESR was 75, well outside the normal range, and the CRP was 1.74, also well outside the normal range. Based on the increase in the ESR and CRP and the symptoms of the patient, giant cell arteritis was presumed to be the diagnosis. The neuro-ophthalmologist started Mr. JA on 80 mg prednisone orally along with an oral proton-pump inhibitor.

Additionally, a temporal artery biopsy was ordered for the left side. The patient's temporal artery biopsy was negative, presumably due to a skip lesion area. Two months later, Mr. JA reported that he had discontinued the prednisone and was feeling terrible. He now had persistent head pain, pain his pelvis and legs, and jaw claudication. He reported that while he was on the prednisone he felt much more like himself. A stat ESR and CRP were also ordered, which revealed that the ESR was 94 and the CRP was elevated to 2.14. Based on the patient's symptoms the patient was re-started on treatment for presumed GCA (80 mg prednisone) even though the temporal artery biopsy was negative. The patient also had a referral placed to see a rheumatologist and to possibly have a repeat temporal artery biopsy. The repeat temporal artery biopsy is usually performed on the contralateral side, even if the first side was negative, especially with cases that have high index of suspicion for giant cell arteritis.

After one week of treatment, Mr. JA reported that he was feeling much better. His headache was almost completely resolved, his jaw claudication had marked improvement, and he had higher levels of energy. He also reported no new visual symptoms. Mr. JA was advised to continue his 80 mg of prednisone as directed and a taper schedule was given for him. He would continue with the 80 mg dosage for another week and then he was to taper to 70 mg of prednisone a day for two weeks. After two weeks of the 70 mg dosing, a repeat ESR/CRP panel would be ordered. After 2 weeks of 70 mg dosage of prednisone, the ESR level was down to 34 and the CRP was down to 0.71. The patient was then tapered down to 60 mg of prednisone/day. The patient's blood glucose was not adversely affected by the high dose of prednisone at that time; the patient was averaging approximately 130 mg/dl at home when checked.

Follow-up#6

Mr. JA then returned to clinic via the emergency department one month later with complaints of a right sided headache that then moved to his left side, involving both the temple and the eye. The patient denied any jaw claudication or scalp tenderness. He did report fluctuating weight, but he was unsure as to whether this was associated with the headache or whether it was because he was eating better. Patient reported no proximal muscle weakness. Mr. JA also had no transient visual obscurations. He reported that although he felt better on the 80 mg of prednisone he is unsure if his headaches were any better. The dosage of prednisone with which he presented to the emergency room was 60 mg. Upon admission to the ER, the patient's prednisone was increased to 80 mg. His vision was still count fingers OD and 20/20 OS best corrected. His confrontation visual fields still showed a severe constriction 360 degrees OD and were full to finger count OS. Mr. JA still had a relative afferent pupillary defect OD. His color plates when tested with Ishihara were 5.5/7 OS only. There was also noted a temporal pulse upon palpation on the right side, with a decreased pulse presence noted on the left side. Also, upon palpation tenderness along the temple area was elicited. No significant changes

in findings were noted on the anterior segment or posterior segment evaluation.

Follow-up#7

The patient returned to the clinic three weeks after discharge from the ER for follow-up with neuro-ophthalmology. He was taking 80 mg/day of prednisone. He complained of poor sleep, weight gain, and poor energy. He still had noticeable scalp tenderness that did not seem to have improved. Jaw claudication was still present, but seemed to have drastic improvement from before. Mr. JA denied any amaurosis or diplopia. His visual acuity and visual field was unchanged from prior visit. He still had a relative afferent pupillary defect OD. Upon palpation, there was still noticeable temple artery tenderness left side greater than the right side. There were no significant changes in findings on either the anterior or posterior segment evaluation. A taper schedule was re-initiated and after a year of treatment, the patient finally reported alleviation of his scalp tenderness and headache. He also had a normal CRP and ESR. Neuro-ophthalmology has continued to monitor, and keeps Mr. JA on a 10 mg dose of prednisone as maintenance.

Discussion

The differential diagnoses in this case include,

- i. Non-arteritic ischemic optic neuropathy (NAION)
- ii. Optic neuritis (ON)
- iii. Giant cell arteritis (GCA)
- iv. Compressive lesion
- v. Migraine

I. NAION has the tendency to occur in patients over the age of 50, with 40% of patients having bilateral involvement. NAION tends to be strongly associated with high cholesterol, smoking, hypertension, diabetes, and heart disease (in decreasing order of associated risk). This condition tends to present as painless vision loss and most often is unilateral with a sudden onset.^{13,15}

II. ON tends to present in young to middle age females and is most often associated with multiple sclerosis. There is usually mild, decreasing vision loss that can go through periods of relapses and recovery. There tends to be pain on eye movement along with decreased contrast sensitivity.^{12,13}

III. GCA tends to present in patients older than 55, with the fellow eye becoming involved in over 75% of cases, with more likelihood of bilateral involvement if no treatment is received within the first two weeks of onset. There is often normal or decreased visual acuity with a RAPD present. There tends to be a central large defect in the visual field. There also can be tenderness on the temporal artery, jaw claudication, headache, cranial nerve 6 palsy, or eye pain associated with this condition.¹⁻¹³

IV. Compressive lesions tend to be asymptomatic in nature, but a patient may complain of decreased visual acuity or color vision. Upon examination proptosis, muscle motility may be disturbed, and the intraocular pressure may be high. Also, the nerve may have pallor or swelling depending on the nature of the lesion.^{12,13}

V. Migraine is characterized by its recurrent nature and the headache that tends to occur. The patient may complain of a unilateral severe headache that often resolves within 72 hours and then may recur. Migraines in the ocular setting are often a diagnosis of exclusion as there are usually no ocular signs that a migraine is occurring or has occurred.¹³

The pathogenesis of giant cell arteritis is an inflammation that predominantly targets large and medium sized arteries only. This particular vasculitis has the tendency to only affect people over the age of 50 and is found more often in women than men. Also, this particular vasculitis tends to only affect those in Western nations, with the highest incidence being in Norway, Iceland, and Sweden. There is a great deal of ongoing research as to whether the vasculitis is truly inflammatory or infectious.^{1-10,14,17,22}

A genetic association has been noted with the HLA-DR4 haplotype, but there is no guarantee that a person who expresses this particular haplotype will develop GCA. Speculation has also been postulated that there may be an association with mycobacterium or Chlamydia pneumoniae or parvovirus; however, there have been no distinct links between any of these infectious agents and giant cell arteritis.^{4,16} Researchers have demonstrated the proposed mechanism for giant cell arteritis in vitro. The proposed mechanism is that there is an antigen, similar to a bacteria or virus that the body recognizes as foreign, within the vessel wall that attracts local t-cell and macrophages, which then promotes the inflammatory response by signaling additional macrophages with pro inflammatory cytokines, like the complement cascade.

Another mechanism is that there is a giant cell that is traveling though the circulation and begins to attack the sclerotic, calcified portion of the arteries, most often on the internal elastic portion. This mechanism accounts for the fact that the majority of patients affected by GCA are all over the age of 50, which is a population that tends to have arteriosclerotic disease of varying degrees.^{1-10,16,20,21} Polymyalgia rheumatica is the only strongly associated systemic condition with giant cell arteritis; this condition tends to affect the joints and muscles in the neck, spine, and pelvic region which manifests as stiffness and pain. 50 percent of patients who have GCA are also symptomatic for polymyalgia rheumatica. Unfortunately, there are no specific tests for polymyalgia rheumatica, so there is little predictive value to be given to this particular condition, unless a patient comes in with this particular diagnosis, which is a diagnosis of exclusion.^{20,21} There are no other systemic conditions strongly associated with giant cell arteritis.

Giant cell arteritis can present itself in a variety of ways. There are two main forms, the systemic and the ocular form; a patient can have one or both of the forms, either simultaneously or after a period of time. The systemic form can manifest itself in an abrupt or gradual manner, most often gradual and subclinical. Giant cell arteritis patients may have a low grade fever along with fatigue and unplanned weight loss, more often associated with the gradual onset. The patients who have the sudden systemic form tend to repeat a high fever with no other known cause.^{1-10,22,23}

Both types of patients often report a severe headache, unlike any one that they have ever had previously. Also, a majority of the patients will report tenderness or decreased pulse pressure upon palpation of the carotid arteries, the temporal arteries, or both. The difficulty for clinicians is being able to tell if the tenderness or decreased pulse

pressure is secondary to giant cell arteritis or due to underlying arteriosclerosis. Finally, the other common systemic symptom is jaw fatigue, especially after long periods of chewing or after changing jaw positions (i.e. switching from singing to being silent).

In a patient presents with the ocular form of GCA, there is likely a complaint of vision loss, eye pain, or double vision.^{1-10,12} Approximately 25 percent of patients who have giant cell will end up with severe visual complication, with irreversible vision loss being found in as many as 15 percent of patients.^{8-10,13} While difficult to truly outguess the course of GCA, if patients have a history of strokes, high levels of clotting factors, or prior history of amaurosis fugax, they are more likely to have lasting visual complications from GCA. Additionally, giant cell arteritis can have severe manifestations in the body as a whole, including aortic dissection or thoracic cavity aneurysms.^{7,8,14}

In order to definitively diagnose giant cell arteritis, certain laboratory tests are warranted. The erythrocyte sedimentation rate and c-reactive protein both need to be run same day, and should be run together to improve sensitivity and specificity. When both of these tests are run together, there is a 99.5 percent sensitivity rate for diagnosis of GCA, compared to 80% each on their own.²⁻⁴ Additionally, there has been new research showing that patients who have been diagnosed with GCA tend to have thrombocytosis, so a great deal of practitioners is now ordering a platelet count in addition to CRP and ESR.¹⁻¹² There is a widespread belief that the platelet count may eventually replace the ESR and CRP for definitive diagnosis of GCA, once more data has been achieved.¹⁰ The newest laboratory test being investigated is the anti-cardiolipin antibody test, which is elevated in giant cell, but is not elevated in other types of systemic inflammation (a disadvantage for both the ESR and CRP). The disadvantage with this particular test is that it is expensive for the patient and there is no normative data published on it.¹⁴⁻¹⁶

Currently, the gold standard for giant cell diagnosis is temporal artery biopsy, which should be completed within 10 days of starting corticosteroid therapy; otherwise the inflammation is likely to start resolving. Unfortunately, with the temporal artery biopsy, there are often skip lesions, so it is possible to get a false negative response. If a false negative response is achieved in a patient who likely has giant cell, a contralateral biopsy is advised. The disadvantages of the temporal artery biopsy are that it is invasive for the patient, the test can yield a high number of false negatives secondary to skip lesions, and the test is only 87 percent sensitive for the condition.^{1-10,12-14} For patients who manifest more ocular symptoms than systemic, fluorescein angiography can be used to assist in diagnosis. With an FA there is usually prolonged choroidal and arterial filling times, which often show areas of non-perfusion or defects in filling.^{1-10,21}

There are several types of treatment options for patients who have giant cell arteritis, with the gold standard being systemic corticosteroids. The reason behind using the corticosteroids is that steroids in general promote anti-inflammation throughout the body, which is a hallmark in patients who have giant cell. There is conflicting information between neurology, ophthalmology, and rheumatology as to the appropriate dosing of corticosteroids, although all the professions do agree that without starting a high dose regimen, progressive vision loss will likely occur.²⁻⁴ There are two treatment options on the corticosteroids, one group tends to recommend oral prednisone at a dose of 1 mg/kg of body weight and the other group recommends admitting a suspected giant cell patient into the hospital for intravenous methyl prednisone for 72 hours-96 hours.¹⁻¹⁰

After starting steroid therapy, a patient will tend to report an improvement in their symptoms within the first week, but it is important for the patients to continue on steroid therapy until their ESR levels return to normal. It can take up to 2 months for the ESR to return to normal levels. The steroids should be tapered, but not according to patient symptoms, rather according to the ESR levels.¹⁻¹⁰ The taper should be approximately 10 percent less than the original dosage every month that they are on it, i.e. a person that starts on 80 mg and has improvement on the ESR markers, can be tapered to 70 mg for one month, then 60 mg and so on.^{1-10,13} The goal is to have the patient on the lowest dose steroid to maintain normal ESR levels and no symptoms for the patient. The greater majority of patients are on steroid treatment for at least two years after the initial episode to decrease relapse likelihood, although some patients are left on a lifetime maintenance dose.^{1-10,13,16}

There have been additional treatments investigated to treat giant cell arteritis, but most pale in comparison to the efficacy of the corticosteroid treatment. Methotrexate, an anti-inflammatory medication, has been studied in combination with prednisone and there has been no additional benefit noted to using methotrexate in combination with prednisone. Also, methotrexate was determined to not be an effective substitute for corticosteroid therapy.^{17,24} Also, Infliximab is an antibody that targets TNF-alpha, which can be found in arteries that have giant cell arteritis. In a randomized trial, patients were started on Infliximab and it was determined that there was no benefit to this medication and it may in fact be causing more harm than good.^{20,25} Finally, aspirin has been evaluated for treatment of giant cell arteritis. Aspirin is beneficial for preventing ischemic events associated with giant cell, but is not effective in removing the source of the inflammation or preventing any other effects of giant cell.^{16,18}

Finally, for the ocular physician, it is important to be able to differentiate between AION related to giant cell arteritis and non-arteritic ischemic optic neuropathy (NAION).^{1-10,26} An AION is an ocular emergency and the goal is to prevent vision loss in the other eye of a patient. Giant cell arteritis tends to present with worse visual acuity compared to non-arteritic ischemic optic neuropathy. Also, GCA tends to have ischemic lesions somewhere in the retina, including central retinal artery occlusions, cilioretinal artery occlusions, or cotton-wool spots.^{15,16,26}

Additionally, patients with giant cell tend to report amaurosis fugax, and may be the only symptom that the patient reports.^{1-8,10-13,20-26} As previously mentioned, fluorescein angiography can also be used to differentiate giant cell from any other ocular causes of vision loss, based on the filling pattern and the defects in filling that will be seen. Upon ophthalmic evaluation, a patient who has giant cell arteritis tends to have chalky white swelling of the optic nerve, which is not found in an NAION. Also, in patients with giant cell there tends to be disc edema associated with either a central retinal or cilioretinal artery occlusion.^{1-10,12,13,16,17} With all of those signs, one would think that diagnosing giant cell arteritis would be straight forward, however, there is an occult form of giant cell arteritis, where patients experience little to no systemic symptoms and vague ocular concerns.⁵

Conclusion

Giant cell arteritis is a potentially blinding condition that all physicians, especially optometrists and ophthalmologists need to be wary of. GCA is one of the few ocular emergencies that need to be appropriately managed and treated immediately. The current standard of care is to run a same day ESR and CRP and a CBC to rule out

confounding factors, and if those come back elevated, the patient needs to be started on systemic corticosteroid therapy, either oral or intravenously. Within a week after starting the steroid therapy, a temporal artery biopsy should be done to confirm presence of giant cell arteritis, and if this biopsy comes back negative, a biopsy on the contralateral side should be performed in patients with likely giant cell arteritis. The patient should continue systemic steroid therapy until there is an improvement in the ESR and CRP, not just an improvement in symptoms.

This particular case represents a combined case of occult and standard giant cell arteritis. The patient exhibited systemic symptoms without any of the ocular manifestations that a physician can see upon clinical examination. The patient at the time of presentation did not have any signs of giant cell on the ESR and CRP, but when he returned for follow-up there was significant increase in these inflammatory markers in his blood stream. He was treated appropriately with systemic steroids and has been followed continuously to ensure that he is on the lowest possible maintenance dose to prevent relapses. This is especially critical in this particular patient as he is essentially monocular secondary to a prior NAION in the fellow eye. It is important for clinicians, and in particular this case, to prevent vision loss in the patient because not only can the vision loss be extreme in the presenting eye, but if left untreated the patient can experience profound vision loss in the fellow eye also. Overall, clinicians need to take reports of any of the systemic symptoms of giant cell and the ocular symptoms seriously and treat these patients as giant cell suspects, while ruling out other conditions.

In retrospect, certain questions can be raised about this particular case, especially regarding the NAION previously diagnosed in the fellow eye. Could this event have been an AION? That is conceivably possible as ESR and CRP were not run at the time of diagnosis of JA's suspected NAION in the right eye. Although unlikely for the effects of giant cell arteritis to not manifest itself in the fellow eye within a few weeks, it is still conceivably possible that Mr. JA had an underlying systemic giant cell arteritis that was not aggressive in its presentation and there was delayed onset of the symptoms in the fellow eye. Based on the patient's medical history, it is likely that Mr. JA had an NAION and would be more at risk for an NAION in the fellow eye secondary to his diabetes and hypertension; however, his systemic symptoms do seem to indicate towards a diagnosis of giant cell arteritis.

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Conflicts of interest

No conflicts to declare.

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