CE Credit - Case Report(s)

Case Report: Giant Cell Arteritis presenting with 6th Nerve Palsy without Ischemic Optic Neuropathy

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Purpose:
Giant cell arteritis (GCA) can be a difficult condition to identify in the early stages especially in the absence of the pathognomonic arteritic anterior ischemic optic neuropathy. Optometrists serve an important role in correctly triaging and initiating appropriate work-up and treatment for this emergent condition. This case report and review serves as a refresher of the systemic and ocular signs and symptoms of GCA.
Background:
GCA is a systemic autoimmune condition characterized by granulomatous inflammation of medium and large arteries in patients over 50. The most well-known constellation of signs and symptoms include new onset headache, jaw claudication, scalp tenderness, temporal artery abnormality with painless vision loss secondary to arteritic anterior ischemic optic neuropathy. However, it is important to be aware of alternate presenting signs and symptoms including pain anywhere in the distribution of the external carotid (occipital, neck, tongue, throat, ear) and signs of large vessel GCA (arm/limb claudication, chest/back pain, Raynaud's phenomenon) and Polymyalgia Rheumatica (PMR) (bilateral hip/shoulder pain and morning stiffness).
Case Report:
An 86-year-old Caucasian female presents for a referred exam regarding new onset diplopia with concurrent occipital headache, neck pain and sore throat originally dismissed as symptoms of her other systemic health conditions. ESR, CRP and platelets were elevated on serology and subsequent temporal artery biopsy was positive for GCA. Oral steroids were initiated, and she was lost to follow up after her ocular symptoms resolved.
Conclusion:
GCA can present with a large range of manifestations, and many are nonspecific and easily attributable to other causes especially when it deviates from the classic constellation of new onset headache, jaw claudication, scalp tenderness and temporal artery abnormality with painless vision loss. Optometrists as primary eye care providers may be the first point of contact and need to be cognizant of the broader set of manifestations to minimize delays in diagnosis and treatment of this life and vision threatening condition.
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INTRODUCTION

Giant cell arteritis (GCA) is a systemic autoimmune condition characterized by the granulomatous inflammation of medium and large arteries found almost exclusively in the over 50+ age group.[1–3] It is the most common form of primary systemic vasculitis in patients over the age of 50.[1,3,4] GCA represents one of the most urgent diagnoses in the realm of eye care due to its life and vision threatening complications.[5] In this case report, we describe the case of an 86 year old Caucasian female presenting with systemic findings consistent with GCA without the classically associated arteritic ischemic optic neuropathy and review clinical features to aid in the diagnosis of this devastating condition.

CASE REPORT

An 86-year-old Caucasian female presented for evaluation and management of a new sudden onset diplopia suspected to be a 6th cranial nerve palsy on the referral of her retina ophthalmologist. Her chief complaint was a sudden onset of constant horizontal binocular diplopia with headaches at the back of the head and neck which began four days ago. The diplopia had not improved or worsened but headaches may have been worsening. She reported no changes to her VA and denied jaw claudication, scalp tenderness and headache near the temporal region. She is pseudophakic in both eyes and had quiescent exudative age-related macular degeneration (AMD) in both eyes receiving injections from the referring retina specialist and has had a total of 14 injections OD and 3 injections OS, the last of which were 1 week and 2 years prior to presentation in right and left eyes respectively. She denied previous ocular infections and trauma. Her systemic history included thyroid dysfunction over 20 years treated with partial thyroidectomy and oral levothyroxine, compound spinal fractures with significant back and neck pain managed with a combination of injection and oral pain medications and a recent onset sore throat which her family physician was treating with oral antibiotics.

Her habitually corrected visual acuity was 20/50 in both eyes, not worsened from previous records. Entrance testing was remarkable for a 10 prism diopter constant left esotropia and 2 prism diopter left hypotropia on distance cover test with her habitual correction. Ocular motility was restricted laterally with approximately 10% reduced range of abduction in the right and 50% reduced range of abduction in the left. Confrontation visual fields were unremarkable. Pupils were equal, round and reactive to light with no RAPD. Intraocular pressures measured by Tonopen were 13mmHg and 10mmHg respectively at 9:31am. Anterior segment evaluation noted mild proptosis in the left and was otherwise unremarkable. Dilated fundus evaluation revealed flat maculae with exudative scarring, geographic atrophy and RPE clumping consistent with her known AMD and optic nerves were unremarkable with no pallor, hyperemia or elevation.

An MRI of the brain and orbits with and without contrast was ordered by the referring ophthalmologist prior to this initial visit. The accompanying radiologist's report noted signal changes consistent with nonspecific small vessel ischemic changes and noted no evidence of intracerebral hemorrhage or significant localized mass effects. The orbits showed borderline bilateral proptosis with mild prominence of the medial rectus muscles bilaterally consistent with her history of thyroid dysfunction. The orbital structures were otherwise symmetric and reasonably maintained with no mass lesion or retrobulbar mass found.

The patient was sent for an urgent referral to the local hospital for blood work including ESR, CRP, lipid panel, CBC and HbA1C, two of which were remarkable - Westergren ESR at 58 mm/hr and CRP at 28.2 mg/L were both significantly elevated. White blood cells, neutrophils and platelet count were mildly elevated. Hemoglobin and hematocrit were mildly reduced. HbA1C and the lipid panel were within normal limits. Based on these findings, a diagnosis of giant cell arteritis was made, and oral steroid medications were initiated and a temporal artery biopsy was ordered within the week which returned positive confirming the diagnosis. The patient's left esotropia resolved over 8 weeks. She was then subsequently lost to follow up.

BACKGROUND

In ophthalmic literature, GCA is often thought of as a cranial disease with the traditional description focusing on the symptoms associated with cranial artery involvement - new onset localized headaches, temporal artery abnormalities (swelling, tenderness, diminished or absent pulse), jaw claudication and ocular complications mainly arteritic anterior ischemic optic neuropathy.[1,5,6] However, more recent classification suggests 3 subtypes of GCA: 1) Cranial GCA as described by the traditional presentation; 2) Large vessel GCA - describing involvement of the aorta and proximal upper and lower limb arteries with common symptoms of arm/limb claudication, back/chest pain and peripheral neuropathy; 3) Polymyalgia Rheumatica (PMR) - describing symptoms clustered at the large muscle groups of the hips and shoulders.[5]

EPIDEMIOLOGY

The annual incidence of GCA is reported between 15-27 per 100,000 in patients over 50 in the US[1,7] and 4.9/100,000 in patients over 50 in Ontario, Canada[8] where the author resides, though the Ontario study is self aware of the deviation from other comparable studies and primarily attributes this to methodological differences. GCA is most common in the elderly with peak incidence between 70-80 years of age.[1,4,7] GCA disproportionately affects Caucasians[1,7] and more so in those of Northern European and particularly Scandinavian descent.[9] There is also a bias towards affecting females at a 2-4:1 ratio to males.[1] There may be a genetic susceptibility component as well with HLA-DRB1*04 and HLA-DR4 found to be more prevalent among GCA patients.[5,7,9]

PATHOPHYSIOLOGY

The pathophysiology of GCA starts with the vascular dendritic cells which reside in the arterial wall and act as antigen presenting cells.[5] When these dendritic cells are inappropriately activated, naive T cells are recruited and differentiated into T helper cells that produce macrophage activating interferons due to the failure of an immune checkpoint that normally prevents this differentiation.[3,10] The macrophages secrete metalloproteinases that break down connective tissue and produce pro-inflammatory cytokines which drive more inflammation and differentiation of immune cells and ultimately lead to luminal occlusion and ischemia.[3,10]

CLINICAL MANIFESTATIONS

The systemic symptoms classically associated with cranial GCA include new onset localized headaches commonly but not exclusively in the distribution of the temporal artery due to abnormalities, scalp tenderness and jaw claudication.[3,5,7] While GCA is also known as temporal arteritis, it is so named for the gold standard diagnostic procedure of temporal artery biopsy and not exclusive involvement of the temporal artery. Cranial GCA can involve any branch of the external carotid and pain symptoms can be in other areas of distribution such as the neck, occipital region, throat, tongue and ears.[4,7] Temporal artery abnormalities may refer to sensitivity to touch (allodynia), irregular contour (beading), prominence or the absence of pulse.[3] In rare cases, patients may exhibit carotid artery tenderness, hearing loss, cerebrovascular strokes or infarction/necrosis of the tongue and scalp.[4,5]

Large-vessel GCA and PMR often phenotypically overlap with classic cranial GCA,[5,7] thus it is important to keep their symptomatology in mind. Large-vessel GCA is most commonly associated with limb claudication, Raynaud's phenomenon and back/chest pain secondary to aortitis/aortic dissection.[5] PMR symptomatology presents more in the large muscle groups of the hips and shoulders with bilateral symmetric pain and morning stiffness for more than 30-45 minutes for longer than 2 weeks.[3,5,7] Constitutional symptoms are also common and are present in all 3 subtypes of GCA.[5,7] These include malaise, fatigue, low grade fever, decreased appetite and weight loss.[4,7]

Ocular manifestations of GCA occur secondary to inflammatory thrombosis causing occlusion of arteries supplying the eye.[4] The most common ocular manifestation of GCA is arteritic anterior ischemic optic neuropathy (AAION) due to the occlusion of the short posterior ciliary arteries (SPCAs) and usually presents with sudden painless vision loss to 20/200 or worse.[7,11] Upon fundus examination, AAION patients may present with a swollen optic disc, retinal hemorrhages and exudates.[7] The optic disc may have pallor early on due to extreme ischemia and will definitely have pallor at late stages due to optic atrophy.[7] In rare instances, the optic nerve ischemia is located posteriorly and no optic disc swelling is observed and the condition is called posterior ischemic optic neuropathy (PION).[7] Optic nerve involvement is an ocular emergency as there is a 54-95% chance of involvement of the other eye within days to weeks if left untreated.[7] Prior to the manifestation of AAION or PION, GCA may present as transient ischemic attacks causing temporary vision loss secondary to partial occlusion of the SPCAs or the central retinal artery.[7] The choroidal ischemia induced by SPCA occlusion can also manifest as an Amalric choroidal infarct, a chorioretinal degeneration usually in a triangular pattern with the apex pointing towards the posterior pole.[4,12] Other ocular manifestations include retinal artery occlusions, ophthalmic artery occlusion, cilioretinal artery occlusion and diplopia.[4] Diplopia occurs in 10-18% of GCA patients and can be attributed to both cranial nerve palsies or muscle ischemia.[4] GCA can cause generalized ocular ischemia, which may lead to neovascularization around the optic nerve,[13] and anterior segment ischemia, which may lead to anterior uveitis, corneal edema, corneal ulceration and hypotony.[14,15] In 20% of GCA patients, only ocular manifestations are observed without systemic involvement. This is known as occult GCA.[7,11]

DIAGNOSIS

Making the diagnosis of GCA can be difficult due to the nonspecific nature of many of the symptoms and its varied and inconsistent presentations.[3] To aid in diagnosis, many guidelines have been considered.

One of the most well-known guidelines for the identification of GCA was the American College of Rheumatology 1990 classification criteria.[16] This guideline highlighted 5 criteria:

1. Age at disease onset greater than or equal to 50 years of age;
2. New onset or new type of localized headache;
3. Temporal artery abnormality including tenderness to palpation, decreased or absent pulsation;
4. Elevated erythrocyte sedimentation rate by Westergren method greater than or equal to 50 mm/hour;
5. Abnormal temporal artery biopsy showing vasculitis with mononuclear infiltration or granulomatous inflammation usually containing multinucleated giant cells.[16]

With these criteria, it was found that if at least 3 of 5 criteria are present, GCA could be differentiated from other vasculitides with a sensitivity of 93.5% and specificity of 91.2%.[16] A critical weakness of using these criteria was its study design was intended to differentiate GCA from other vasculitides, not diagnose GCA.[5,10] To address this, Dejaco et al suggested additions to 4 of the original 5 criteria:

2. New onset or new type of localized headache or visual symptoms, sight loss, PMR, constitutional symptoms, Jaw and/or tongue claudication;
3. Abnormality in any extracranial artery not just the temporal artery;
4. ESR greater than or equal to 50 mm/hour and/or CRP greater than or equal to 10 mg/L;
5. abnormal temporal artery biopsy and/or abnormal imaging result using ultrasound, MRI and/or PET.[5]

Notably, as the authors themselves point out, these are opinion-based recommendations and have not been vetted

Clinical Features of GCA and frequency reported in literature

Clinical Features of GCA	Frequency/ Other key notes
Elevated ESR and/or CRP	90-95%[1]
Headache, new onset, localized	70-90%[1] 66%[5] • most commonly but not exclusively in the temporal region[1,7]
Audiovestibular manifestations[1,2,7]: • hearing loss • vertigo or abnormal vestibular testing • tinnitus • ear pain	Up to 90%[1,2]
Polymyalgia Rheumatica[1,2,5,7]: • Severe and bilateral pain associated with morning stiffness greater than 30 minutes in 2 of 3 key areas: 1) Neck, 2) Shoulders or 3) pelvic girdles/hips • Constitutional symptoms	40-60%[1] 45-61%[5] • Ask about trouble getting out of a chair or reaching for objects above shoulder height, e.g. cupboards[7] • Most common extracranial symptom[3] • Most frequent symptom of relapse (~50%)[5]
Constitutional symptoms[1,5,7]: • fever - typically low grade but as high as 40ºC • Malaise/fatigue • Poor appetite/weight loss • Depression	30-60%[1] <50%[5]
Abnormal temporal artery[1,3,7]: • Sensitivity to touch/allodynia • Absent/diminished pulse • Irregular contour/beading • Prominence	30-60%[1] 66%[3]
Jaw claudication	40-50%[1] ~50%[5] • Most specific symptom[1,7] • Note that jaw claudication is the pain associated with mastication (i.e. chewing) and deglutition (i.e. swallowing) and not a constant jaw pain[7,16]
Scalp tenderness	33-50%[1] • This symptom is often best elicited by asking about pain when brushing hair[7]
Visual disturbances, transient or permanent	20-50%[1] 20-30%[5]
Out of 84 consecutive patients with vision loss and temporal artery biopsy proven GCA,[6] the diagnoses were as follows:	
Arteritic Anterior Ischemic Optic Neuropathy	91%
Central Retinal Artery Occlusion	10.5%
Cilioretinal Artery Occlusion	10%
Posterior Ischemic Optic Neuropathy	4%
Diplopia presumed secondary to paresis or muscle ischemia	10-18%[4] 6-27%[3]
Respiratory symptoms[1] • Cough • Sore throat • Hoarseness	10%[1]
Cerebrovascular accidents[1]: • Transient ischemic attacks • Stroke	3-7%[1]
Scalp necrosis	<5%[1]
Tongue necrosis/pain	<5%[1]
Large Vessel GCA symptoms[5] • intermittent arm/limb claudication • back/chest pain (secondary to aortitis/aortic dissection) • Raynaud's phenomenon	Frequency of occurrence with cranial GCA not reported in consulted literature

ESR	CRP	Platelets
Miller: 76.5-86% sensitive; 94% specific • Men: [age/2] • Women: [(age + 10)/2] Hayreh: 85.7-94% sensitive; 80-90% specific • Men: [17.3 + 0.18 * age] • Women: [22.1 + 0.18 * age]	Costello: 98.6% sensitive and 75.7% specific >5mg/L	Costello: 57% sensitive; 96.5% specific >400 x 10^3/uL
When ESR and CRP are used together (elevation of either or both markers by the above criteria): 99.2% Sensitive		
Ing's prediction modeling did not threshold criteria and instead considered blood work as a continuous variable; this approach made platelets a better predictor than even ESR/CRP		

by a peer-reviewed study. Another attempt to remedy the lack of guidance in the diagnosis of GCA was the generation of 2 prediction models using logistic regression and neural networks which provides the pre-test probability (prior to temporal artery biopsy or ultrasound) of GCA when provided with a list of predictors: age, gender, new onset headache, clinical temporal artery abnormality, jaw claudication, permanent retinal, optic nerve or visual pathway ischemic vision loss, diplopia, pre-steroid erythrocyte sedimentation rate, pre-steroid C-reactive protein divided by the upper limit of normal for vasculitis for each lab, and pre-steroid platelet level.[17] These 2 prediction models used 1,201 cases from 14 international medical centers making it the largest pool of data used for prediction modeling to date according to the author.[17] When both models are used together it was able to achieve a 99% sensitivity.[17] The authors have made the risk calculator available for free at https://goo.gl/THCnuU for those practicing with the scope of practice to order blood work and sufficient access to do so emergently.

When ordering blood work for suspected GCA, the most important markers are ESR, CRP and platelet levels. However, when it comes to determining the cut off for normal or elevated markers, different cut offs are suggested.

In the evaluation of ESR, it's often taught that the upper limit of normal range should be calculated as [age/2] for men and [(age + 10)/2] for women based on a recommendation by Miller et al in 1983 suggested on the basis that only 2% of the normal population between age 20 to 65 would be captured using this target.[18] When this criteria was tested against 106 biopsy proven GCA cases out of 363 temporal artery biopsies ordered in an ophthalmic practice, it was found to have a sensitivity of 86% and specificity of 94% whereas Hayreh et al's calculation of [17.3 + 0.18 * age] in men and [22.1 + 0.18 * age] in women yielded a sensitivity of 92% and specificity of 92%[19] and in a subsequent study by Costello et al comparing 121 GCA patients to 287 NAION patients, Hayreh's formula yielded 94.2% sensitivity and 80.5% specificity.[20] In another ophthalmology study by Parikh et al with 199 biopsy proven GCA cases, Miller's formula was 76.5% sensitive and Hayreh's formula was 85.7% sensitive.[21] A larger study from rheumatology by Kermani et al with 177 biopsy proven GCA cases out of 764 temporal artery biopsies ordered in a general practice suggested an optimal cut off of 53mm/hour for a sensitivity of 66% and specificity of 55%.[22]

In the evaluation of CRP, Kermani et al suggested an optimal cut off of >26.9mg/L for a sensitivity of 75% and specificity of 51%[22] and this echoed previous work by Hayreh et al that suggested >24.5mg/L.[19] In the Costello GCA vs NAION study, a CRP cut off of 5mg/L was found to be 98.6% sensitive and 75.7% specific.[20] This cut off was found to be 97.5% sensitive in the Parikh study.[21] When both ESR and CRP are used together and the elevation of either or both markers (ESR by either Miller or Hayreh's formula and/or CRP over 5mg/L) be considered a positive finding, the sensitivity was found to be 99.2%.[21] Despite the sensitivity of these inflammatory markers used together, a small number of cases have been reported with both normal ESR and CRP.[23]

In the evaluation of platelets, the Costello study found a cut off of 400 x 10^3/uL to be 57% sensitive and 96.5% specific.[20] However, in Ing et al's prediction modeling, elevated platelets levels were a stronger predictor of GCA than even ESR/CRP when bloodwork was maintained as a continuous variable instead of binary outcomes of above or below a cut-off as previous work had done.[17]

The gold standard for the diagnosis of GCA remains the temporal artery biopsy (TAB), typically of a section 2-3 cm in length to avoid skip lesions(areas of discontinuous arterial involvement).[3,7] A TAB is considered a positive result when a chronic granulomatous inflammation centered on the internal elastic lamina is detected.[3] A TAB has been reported to have 99% specificity but may have as low as 39% sensitivity due to poor sampling (7% of TABs are estimated to not contain the arterial tissue of interest) and poor agreement between pathologists (one study demonstrated that of 30 cases reviewed by 14 pathologists, only 11 cases found unanimous agreement between all 14).[1,3] Due to the severe morbidities associated with GCA, steroidal medications may be initiated on suspicion and/or from laboratory testing prior to the temporal artery biopsy. Therefore, it is ideal to retrieve the pathologic specimen within 2 weeks of steroid initiation while the treatment effect has minimal impact on the diagnostic value of the test. However if this cannot be achieved a TAB still has diagnostic value beyond the 2 week point as studies have shown positive biopsies even after use of steroid medication for 3 to 9 months.[7,24] While the diagnostic value of a TAB is indispensable, clinicians should be aware of the invasive nature of the procedure and, while infrequent, complications can occur. One study including 75 biopsies showed a complication rate of 22%, which included extensive ecchymosis (5.33%), infec-

tion (2.67%) and brow ptosis (16%) secondary to iatrogenic damage to the frontal or temporal branches of the facial nerve.[25] Complete resolution of brow ptosis was achieved in 58% of their study group.[25]

Adjunctive imaging modalities have been used to characterize GCA patients. These include fluorescein angiography (FA), Indocyanine green angiography (IGA) and OCT angiography assessing ocular perfusion and ultrasound, MRI, CT and PET assessing systemic perfusion. Of these, the most relevant to optometry are the ocular perfusion modalities and ultrasound as the most readily accessible point of care imaging modality. In AION patients, choroidal hypoperfusion can be visualized in an FA with a significantly delayed choroidal filling time at a mean time of 69 seconds versus 5.5 seconds in non-arteritic anterior ischemic neuropathy and 8-12 seconds in normal patients.[24] In IGA, it will appear as an area of hypocyanescence and in OCTA it will appear as an area of flow deficit.[12] OCTA has the advantage of not requiring dye but has the disadvantage of having a much smaller area imaged per acquisition and may require stitching together multiple acquired images into a montaged image to obtain a broad assessment comparable to dye based modalities.[12] Vascular ultrasound looking for the "halo sign", a non-compressible hypoechoic ring around the arterial lumen representing edema/thickening of the arterial wall, has been reported to have 55-100% sensitivity and 78-100% specificity.[3] The ultrasound halo sign is sensitive to glucocorticoid treatment with the sign diminishing and vanishing over 2-10 weeks of treatment.[1] This technique is operator and machine dependent which may account for the wide range of reported sensitivity/specificity and the recommendation that TAB still be considered in ultrasound negative cases.[1] However, ultrasound is generally low cost and rapidly accessible which makes it the first imaging modality of choice.[1]

TREATMENT AND MANAGEMENT

Treatment for GCA typically consists of high dose steroids over several months or longer with some debate over the route of delivery and dosage with some clinicians suggesting patients with vision loss be started on IV steroid 1g/day for the first 3 days while others advocate oral steroid at 1mg/kg/day is sufficient to prevent further vision loss.[24] Chronic steroid therapy can have significant side effects including increased risk of infections, diabetes, hypertension, gastric ulcers, and osteoporosis, and so referral to an internist to monitor systemic health is recommended.[24] During the steroid taper, there is a chance for the GCA to relapse, necessitating further steroid use.[24] Adjunctive therapies involving immunomodulatory agents such as methotrexate have also been investigated.[24]

CONCLUSION

GCA can present with a large range of manifestations, and many are non-specific and easily attributable to other causes especially when it deviates from the classic constellation of new onset headache, jaw claudication, scalp tenderness and temporal artery abnormality with painless vision loss. Furthermore, GCA is an uncommon condition and primary care providers may not be reviewing the symptomatology of GCA on a routine basis. In this case, the patient's sore throat was treated as a bacterial etiology and her neck pain was attributed to prior spinal fracture. Optometrists as primary eye care providers may be the first point of contact for these cases and need to be cognizant of the broader set of manifestations to minimize delays in diagnosis and treatment of this life and vision threatening condition.

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