Interdisciplinary approach in the management of visual loss in giant cell arteritis

Luca De Simone[1†], Chiara Marvisi[2†], Caterina Ricordi[2], Fabrizio Gozzi[1], Elena Bolletta[1], Pietro Gentile[1,3], Francesco Muratore[2], Luca Cimino[1,4], Carlo Salvarani[2]

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Abstract:

Giant cell arteritis (GCA) is the most common vasculitis among older patients in western countries. A correct diagnosis permits the prompt initiation of glucocorticoids, which still represent the cornerstone of treatment. One of the most feared complications of the disease is sudden visual loss and other ischemic events causing visual disturbances. In these cases, an interdisciplinary approach between ophthalmologists and rheumatologists is crucial to avoiding any diagnostic delays and to permitting correct clinical assessment without subjecting the patient to unnecessary treatment. In this review, we discuss the main causes of visual disturbances in GCA, particularly the causes of sight loss, outlining the red flags that should raise suspicion in ophthalmologists and rheumatologists.

Keywords:

Giant cell arteritis, ophthalmologist, rheumatologist, vasculitis, visual loss

Introduction

Giant cell arteritis (GCA), also known as temporal arteritis, is the most common vasculitis in individuals over 50, peaking around the 8th decade, with a female predominance (3:1 female-to-male ratio). It is classified as a large-vessel vasculitis involving medium- to large-size arteries, with a preference for the aorta and its main branches. It can cause a wide spectrum of clinical manifestations, depending on the affected arterial territory. The involvement of extracranial branches of the external carotid artery gives rise to the classic cranial symptoms of the disease such as new-onset headache, jaw claudication, and visual symptoms. The most feared disease complication, observed in up to 30% of newly diagnosed GCA patients, is permanent vision loss, which may be partial or complete. Glucocorticoids (GCs) should be promptly started when visual manifestations occur to prevent further visual loss. Indeed, the contralateral eye, if untreated, may be affected soon after (1–14 days) the first ischemic event.

In this review article, we summarize the most common causes of visual loss in GCA and outline the red flags that rheumatologists and/or ophthalmologists should be aware of to avoid diagnostic delays and to permit the prompt initiation of appropriate treatment.

Visual Loss in Giant Cell Arteritis

Visual loss is one of the leading causes of morbidity related to GCA. Studies conducted before the advent of GC treatment showed a high prevalence (35%–60%) of visual complications,[1] whereas those performed after the broader use of GCs detected much lower rates of sight loss (about one in six patients). Older patients (>80 years old) present a higher risk of developing ischemic symptoms, including visual loss.[2] Ocular ischemic events are generally associated with GCA if they occur concomitantly with GCA or within 4 weeks after the onset of GC therapy.[3-5] In most cases, visual loss is an early event that occurs before, or within a few days of, the onset of GC treatment.[6,7]

Risk factors for ischemic events

Several studies have addressed the role of risk factors in the pathogenesis of GCA-related ischemic events. A previous cranial ischemic event is considered one of the strongest predictors

[1]Ocular Immunology Unit, Azienda USL-IRCCS di Reggio Emilia, [2]Rheumatology Unit, Azienda USL-IRCCS di Reggio Emilia, and University of Modena and Reggio Emilia, [3]PhD Program, University of Modena and Reggio Emilia, [4]University of Modena and Reggio Emilia, Italy
†These authors contributed equally to this work.

Address for correspondence:
Dr. Luca De Simone, Ocular Immunology Unit, Azienda USL-IRCCS Di Reggio Emilia, Viale Risorgimento 80, Reggio Emilia 42123, Italy.
E-mail: luca.desimone@ausl.re.it

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for a subsequent event.[8-11] The presence of ischemic symptoms like jaw claudication, which is thought to be ischemic in origin, can also predict subsequent ocular ischemic lesions. Compared to patients with cranial GCA, those with large-vessel GCA, who present less often with cranial symptoms including jaw claudication, have a reduced frequency of visual loss (4% vs. 11%).[12]

Other cardiovascular comorbidities also play a role in considering a patient at higher risk. The presence of hypertension before the onset of GCA has been reported as a risk factor for severe ischemic complications in patients with biopsy-proven GCA. This has subsequently been confirmed in some studies.[13] In an Italian population-based cohort study, hypertension, previous ischemic heart disease, and low levels of inflammation were associated with a higher risk of the occurrence of ischemic events in GCA.[4] Another study found a positive association between traditional risk factors for atherosclerosis and GCA-related ischemic events, suggesting that patients with atherosclerosis might be unable to efficiently mount appropriate angiogenic compensatory mechanisms.[13] Moderate, but not excessively high, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels at the time of diagnosis are predictors of irreversible visual loss. In contrast, markedly elevated ESR and CRP as well as anemia are linked to a decreased risk of ischemic events.[4,13]

Clinical Conditions Associated with Visual Loss in Giant Cell Arteritis

Anterior ischemic optic neuropathy

Anterior ischemic optic neuropathy (AION) is the most common ocular manifestation of GCA. Ischemia typically occurs in the intrabulbar portion of the optic nerve, leading to optic disc edema (ODE) during the acute phase, known as arteritic AION (A-AION). It is caused by infarction of the anterior prelaminar layer of the optic nerve due to occlusion of the short posterior ciliary arteries (PCAs). When ischemia occurs further along the optic nerve in the retrobulbar segment, it results in impaired visual function without ODE during the acute phase. This less common condition is called arteritic posterior ischemic optic neuropathy (A-PION or simply PION).[14]

Clinically, A-AION is often preceded by amaurosis fugax or premonitory transient monocular vision loss (TMVL). These symptoms can occur due to incipient ischemia of the retina or optic nerve due to a reduced blood flow to both the anterior and posterior segments of the eye. This diminished perfusion places the retina in a precarious metabolic state, potentially leading to recurrent episodes of very brief (lasting seconds) amaurosis. However, retinal ischemia presenting with sudden visual loss is more common.

Both forms of ischemic optic neuropathy must be differentiated from the more prevalent non-A-AION (NA-AION), which typically presents with ODE.[15]

In the acute phase, A-AION causes a pale appearance of the optic nerve head along with ODE [Figure 1]. This combination is unusual as ischemia from NA-AION typically causes ODE in the acute phase and pallor in the chronic phase. With A-AION, the pallor of the optic disc becomes more apparent as the edema resolves and retinal ganglion cell axons are lost. In some cases, the aggressive arteritic process can lead to late cupping of the optic nerve head, in contrast to NA-AION, where the optic nerve head cup is characteristically crowded. Thus, ischemic optic neuropathy in one eye and a relatively large optic disc cup in the other eye should raise suspicion of GCA.[16]

In A-PION, ischemia of the retrobulbar portion of the optic nerve does not change the appearance of the optic disc during the acute phase. However, in the late stage, optic nerve pallor becomes evident, as is true for any disorder causing significant damage to the optic nerve fibers.[17]

Amaurosis fugax and occipital lobe infarct

GCA is a very rare cause of stroke, which typically affects the vertebrobasilar territory and is the leading cause of mortality.

Cortical blindness usually leads to a complete and permanent impairment of vision, unlike NA-AION, which often causes an altitudinal deficit. In this clinical scenario, patients may also present with TMVL as a result of embolization. Such events may occur repeatedly throughout the day, with a much higher frequency and shorter duration than TMVL.[18,19]

Central retinal artery occlusion

Arteritic central retinal artery occlusion (CRAO) affects around 12% of eyes of GCA patients.[3] CRAO leads to significant visual loss, more aggressive than that typically observed with nonarteritic CRAO from any cause.[20] The earliest funduscopic indication of any CRAO is the blunting of choroidal pigmentary detail in the macula due to retinal edema with the appearance of the classic cherry-red spot associated with box-carring of the flow through the retinal vessels.[18] The central retinal artery typically originates from the ophthalmic artery, usually sharing a common trunk with one or the other PCAs. In cases of concomitant CRAO and PCA occlusion, the classic cherry-red spot disappears due to

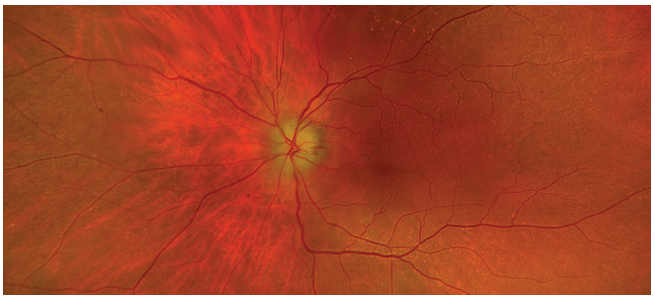

Figure 1: Left eye color fundus photography of a 76-year-old female patient with an acute arteritic anterior ischemic optic neuropathy: Optic disc edema (ODE) appears with a swollen optic nerve head with blurring margins and flame-shaped peripapillary hemorrhage; note the typical pale appearance of the optic nerve head along with ODE

reduced perfusion of the choroid and the absence of the visual contrast between the edematous retina surrounding the fovea and the retained choroidal perfusion beneath the retina. In this case, fluorescein angiography (FA) evidence of PCA occlusion is highly suggestive of GCA.[21]

Cilioretinal artery occlusion

Cilioretinal arteries are anatomical variants found in approximately 25% of the population that can supply nourishment to the nasal part of the macula. Originating from the PCA system, they can help preserve a small part of central vision in cases of CRAO. In GCA, a combination of ODE A-AION and retinal edema (whitening) in the area of the occluded cilioretinal artery is a devastating condition for the patient's sight and is usually due to PCA occlusion, as evidenced by FA.[21]

Cotton wool spots

In GCA, one-third of affected eyes exhibit retinal cotton wool spots at the posterior pole, indicating focal retinal ischemic lesions[3] [Figure 2].

Diplopia

Diplopia is reported in ≤10% of patients and is typically transient.[22] According to the myogenic theory, it can be secondary to the arteritic occlusion of one or more of the arteries supplying the extraocular muscles.[21,22] On the other hand, the neurogenic theory supports the possibility that the diplopia can be secondary to a sixth nerve palsy, although a third nerve, or more rarely, a fourth nerve palsy may occur as well. GCA diplopia may ultimately result as a manifestation of a brainstem stroke.[18,22]

Diagnosis of Giant Cell Arteritis

One of the most challenging situations in diagnosing GCA for rheumatologists and ophthalmologists is a patient with visual symptoms at the onset of the disease. In this case, the timing for initiating the correct treatment is crucial to avoid further complications. On the other hand, an incorrect diagnosis could expose the patient to unnecessary high doses of GCs and adverse events.

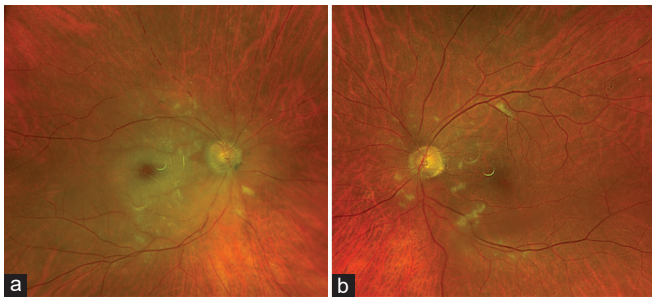

Figure 2: Color fundus photography of a 79-year-old patient diagnosed with giant cell arteritis. The right eye (a) shows characteristic signs of central retinal artery occlusion, including retinal edema with the typical cherry-red spot, segmentation of blood flow within the retinal vessels, and attenuation of the retinal arteries. The left eye (b) exhibits cotton wool spots around the optic disc, indicating focal retinal ischemic lesions

From a clinical point of view, clinicians should look for signs and symptoms related to the cranial involvement of GCA such as headache, jaw claudication, and constitutional symptoms. A history of polymyalgia rheumatica should raise suspicion that the visual symptoms may be secondary to GCA. These patients should undergo laboratory studies, including a complete blood count (to check for unexplained anemia or elevated platelet count), ESR, and CRP.[23]

According to the latest American College of Rheumatology and EULAR guidelines, temporal artery biopsy (TAB) and/or temporal artery imaging are recommended in all patients presenting signs or symptoms compatible with GCA, especially those with cranial ones.[24,25] TAB is a minimally invasive surgical procedure performed under local anesthesia in an outpatient setting generally associated with a low risk of complications. TABs test positive in around 25%–35% of suspected GCA cases.[24] If GC therapy has already been started without the histopathological diagnosis, it is advisable to perform TAB no later than 2–4 weeks from GC initiation to maximize the diagnostic yield.[26] Unilateral TAB is the standard approach, but in negative cases and persistently high clinical suspicion, bilateral TAB can be performed considering the possibility of "skip lesions."[27] The classical histopathological picture of GCA is characterized by transmural inflammation, causing disruption of the internal elastic membrane, and various degrees of intimal hyperplasia.[23] About 50% of TABs with TMI present a granulomatous inflammation with giant cells at the intima-medial junction; in the remaining 50% of cases, inflammatory infiltrate is composed of lymphomononuclear cells, even if neutrophils and eosinophils can also sometimes be observed.

CDS of the temporal arteries has shown good sensitivity and specificity for the diagnosis of GCA when performed by expert operators, and in that case, it can be considered a diagnostic surrogate of TAB.[28] Indeed, according to the fast-track approach, all patients with cranial symptoms suspected of GCA should undergo a CDS; if this results positive, the diagnosis of GCA can be made. In cases of high clinical suspicion of GCA but negative or uncertain CDS, TAB is recommended anyway. The fast-track approach contributed to a substantial reduction in permanent visual loss in GCA by shortening the time to diagnosis and treatment initiation.[29] The halo sign, defined as a hypoechoic wall thickening which remains unvaried upon compression, represents the pathognomonic ultrasonographic finding of GCA[30] [Figure 3].

Other imaging techniques may be employed in the diagnosis of GCA, but they often require more time, making them less suitable compared to CDS in the fast-track approach for patients with visual symptoms. In particular, new-generation positron emission tomography/computed tomography has been exploited to assess cranial arteries (temporal, maxillary, occipital, and vertebral arteries), showing good sensitivity and specificity for GCA diagnosis.[31,32] Mural thickness and contrast enhancement of the scalp arteries indicating vasculitis

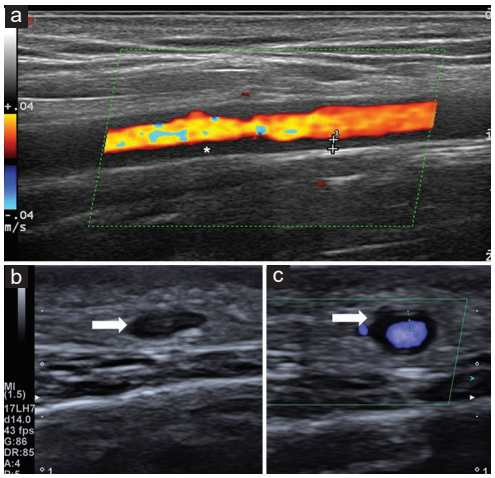

Figure 3: Typical color Doppler sonography findings in cranial giant cell arteritis. Halo sign around the temporal artery on longitudinal view (white asterisk, a) and transverse view (white arrows b and c). The halo sign indicates inflammation of the vessel wall and remains visible after compression of the vessel (b)

can be visualized on magnetic resonance angiography. Lately, intraorbital magnetic resonance has been recognized as an interesting tool to detect subclinical inflammation of orbital structures in GCA patients since enhancement of optic nerve sheaths has been observed independently of ocular symptoms.[33]

Management of Giant Cell Arteritis

GCs represent the standard of treatment in GCA. Initial GC dose ranges between 40 and 60 mg/day of oral prednisone equivalent or 500–1000 mg/day of intravenous (IV) methylprednisolone for 3 days, followed by oral 1 mg/kg/day of prednisone equivalent; the latter therapeutic scheme is preferred in patients at higher risk of cranial ischemic events.[25,34,35] Once disease control has been achieved, tapering of the initial GC dose by 10 mg every 2 weeks to a target dose of 15–20 mg/day within 2–3 months is recommended.[25] The development of visual loss rarely occurs after initiation of high-dose GCs, but visual acuity of the initially affected eye may worsen in up to 30% of patients in the 1st week from starting GC (either oral or IV).[36-38]

As far as visual improvement is concerned, a study by Hayreh *et al*.[39] showed that only 4% (5 out of 114) of eyes with visual loss due to GCA improved in visual acuity and central visual field, suggesting that GC therapy is seldom able to improve the visual loss caused by GCA. There was also no evidence that GC pulse therapy was more effective than oral therapy in visual improvement.[4]

Other studies have reported a higher percentage of visual acuity amelioration (up to 34% of cases) soon after GC treatment. However, in these studies, the increase in visual acuity, without a corresponding improvement in the central visual field, may just reflect a better accommodation capability and not a real visual recovery.[40,41]

In any case, GCs are able to prevent visual loss in GCA, an event that can occur in the second eye in around 30% of patients within 1–14 days.[17,18] In 91 patients with visual loss and 53 patients without visual loss, followed for at least 2 weeks while on high doses of GCs, only nine patients developed further visual acuity deterioration in one or both eyes within 5 days after the start of therapy, while none of the 53 patients without visual loss developed any visual deterioration.[14]

IV GC pulse therapy followed by high-dose (80–120 mg) oral prednisone can be commenced in patients who present with a history of amaurosis fugax or complete or partial loss of vision. If GCs have represented the cornerstone of GCA treatment, the numerous side effects related to prolonged GC treatment indicate the need for alternative therapeutic agents.

Among conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs), methotrexate (MTX) can be considered in the treatment of relapsing GCA.[24] In spite of favorable data on the GC-sparing potential and on relapse rate reduction provided by the early introduction of MTX, there is no supporting evidence of the efficacy of MTX in reducing visual complications in newly diagnosed GCA patients.[42-44] Indeed, in a randomized placebo-controlled trial, no difference in the development of vision loss was observed in the group receiving MTX versus the placebo arm, with an overall rate of new visual loss of 13.8% after 1 year of follow-up.[43]

The introduction of tocilizumab (TCZ), a recombinant monoclonal antibody directed against interleukin 6 receptor (IL-6R), is recommended either from disease onset or at relapse according to different guidelines.[24,25] TCZ efficacy in inducing and maintaining disease remission has been proven by two randomized placebo-controlled trials.[45,46] In these two trials, TCZ demonstrated a good GC-sparing potential since by weeks 26 the Giant-Cell Arteritis Actemra (GiACTA) trial and 36, respectively, GC was discontinued.[45,46] In the GiACTA trial, one patient (1/49) receiving TCZ every 2 weeks, together with the reduced GC tapering scheme over 26 weeks, presented a disease flare with AION. In the GUSTO trial, which was an open-label trial on the use of TCZ monotherapy after only 3 days of IV GC, 1/18 patient developed visual loss due to AION.[47] Despite the role of reducing overall disease flare, there are still insufficient data to propose TCZ in monotherapy, especially when cranial ischemic manifestations are present. According to just observational studies, the addition of TCZ to GC treatment early in the disease course may have a protective effect on the development of visual complications.[48,49]

Among newly proposed DMARDs, the anti-IL17A secukinumab and the Janus kinase 1 and 2 inhibitor baricitinib have been tested for GCA treatment in a root canal treatment and an open-label pilot study, respectively.[50,51] Results of these two studies are encouraging, but their impact on the cranial pheno of the disease has not been clearly assessed.

Antiplatelet therapy such as low-dose aspirin given either for primary or secondary prophylaxis has not had a definite effect

on the risk of cranial ischemic events according to different retrospective studies.[4,52-54] Since the risk of bleeding may overcome the unknown beneficial effect on inflammatory vessel disease, indication to antiplatelet therapy should follow the general recommendations for cardiovascular prevention.[55]

Conclusion

GCA is the most common vasculitis in adults over the age of 50 years old. Around 30% of patients may present with sudden visual disturbances at disease onset. Ophthalmologists and rheumatologists should always consider GCA among differential diagnoses in all these cases. Findings at fundoscopy may guide the ophthalmologist who, in suspected cases of GCA, should order laboratory exams and a rheumatology consult. The rheumatologist has the role of diagnosing GCA (by TAB, CDS, or other imaging techniques) and initiating treatment. It is important to underline that in all cases of sight loss (occurring in up to 30% of patients), high doses of GCs should be started quickly to avoid any further disturbances in the contralateral eye. Hence, an interdisciplinary approach is crucial to permit a prompt and correct diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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