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WHEN THE PICTURE MASKS THE DIAGNOSIS - AN ATYPICAL AND SEVERE GIANT CELL ARTERITIS CASE REPORT

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Purpose: The purpose of this study was to describe an atypical and severe case of giant cell arteritis (GCA).

Methods: This was a case report description.

Results: The authors report the case of a 76-year-old man who presented with severe and progressive bilateral visual loss. On presentation at the ophthalmology emergency room, the patient's right eye (OD) displayed aqueous flare, hyphema, *rubeosis iridis*, and dense posterior capsular opacification. After YAG laser capsulotomy, vitreous densifications, intraretinal hemorrhages, cotton wool spots, retinal ischemia, and vasculitis were observed in the fundoscopy. The patient's left eye (OS) also presented intraretinal hemorrhages and cotton wool spots around the temporal arcades. The diagnostic workup excluded infectious diseases, demyelinating diseases, and ocular ischemic syndrome due to carotid obstruction. Proteinogram revealed a monoclonal gammopathy, suggesting a possible hematologic condition. High-dose corticotherapy was initiated, which improved the vitreous densifications and enabled the visualization of the pale optic disk. The remaining study did not confirm the diagnosis of hematologic disease. During follow-up, bilateral VA deteriorated, with the development of progressive pallor in the OS optic disk. Follow-up fluorescein angiography demonstrated progressive retinal and choroidal ischemia. Finally, owing to high clinical suspicion, temporal artery Doppler ultrasound was performed, confirming the diagnosis of GCA.

Conclusion: GCA may present multiple ocular features. The knowledge of these different presentations, including retinal and choroidal ischemia or uveitis, is critical for timely diagnosis and treatment initiation. Since patients with GCA often present with vision loss, ophthalmologists may be the first medical doctors who contact with these patients, being on the frontline of GCA diagnosis.

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Giant cell arteritis (GCA), a granulomatous medium and large vessel vasculitis, constitutes the most common vasculitis in adults.[1] It is more frequent in older patients, women, and White people. Smoking, low body max index, and early menopause have also been reported as risk factors.[2] GCA etiology is not completely understood, although genetic and environmental factors such as infections have been postulated as predisposing factors.[1] Regardless of etiology, GCA is characterized by an inflammatory response against specific antigens in medium and large arteries,[1] leading to a granulomatous response and consequent vessel wall thickening, luminal occlusion, ischemia, and ultimately organ damage.[1]

External cranial branches of the aorta constitute the most frequently affected vessels. Lesion of these vessels leads to focal ischemic complications causing low vision or jaw claudication. Simultaneously, the inflammatory cascade mediates fever, headache, myalgias, anorexia, and weight loss.[1]

Regarding ophthalmic manifestations, visual loss is frequently caused by arteritic anterior ischemic optic

neuritis (AAION).[1,3] However, choroidal infarction, central and branch retinal artery occlusions, and posterior ischemic optic neuropathy may also occur, albeit less frequently.[1]

GCA diagnosis relies on a complete history and physical examination allied to complementary examinations, including serologic inflammatory markers, pathologic abnormalities on temporal artery biopsy, and/or evidence of large vessel involvement on vascular imaging.[1,3]

Early detection is critical for ensuring timely treatment and avoiding complications. However, the nonspecific nature of some symptoms, as well as the wide range of clinical phenotypes, makes GCA a challenging diagnosis in some cases. We report a case of severe GCA with an atypical ophthalmic presentation. Awareness of GCA's diverse clinical presentations is required to be able to have a high clinical suspicion and perform a timely diagnosis with prompt treatment initiation.

Case Report

A 76-year-old man presents to the ophthalmology emergency room (ER) with a history of progressive VA reduction in the right eye (OD) over a six-month period, with sudden worsening in the past 24 hours. He presented a medical history of type 2 diabetes, hypertension, dyslipidemia, active smoking, and a previous stroke with no sequelae. In addition, he was regularly observed in the Internal Medicine Outpatient Clinic due to anemia and asthenia, for which he was being studied and was receiving iron supplements. The patient's ocular history included bilateral cataract surgery performed three years prior in another institution. Clinical records mentioned a dense right cataract, with almost 360° posterior synechiae. After cataract surgery, the OD fundoscopy revealed dispersed hemorrhages and cystoid macular edema, treated with one triamcinolone intravitreal injection. No complications or other intercurrences were described for the left eye (OS). No further investigation was performed, and the patient abandoned the follow-up in that hospital. The best-corrected VA (BCVA) after surgery, two years before coming to our ER, was 20/30 on the OD and 20/20 on the OS.

In the ER, the OD BCVA was counting fingers and the OS BCVA was 20/25. Biomicroscopy revealed OD endothelial brown pigment deposition, aqueous flare, a fine line of hyphema in the anterior chamber, *rubeosis iridis*, a nonreactive mid-dilated pupil, pseudophakia, and a dense posterior capsule opacification; the patient's OS was pseudophakic and presented no other remarkable findings. Both eyes presented normal intraocular pressure. The OD fundoscopy was impossible due to the posterior capsule opacification. After YAG laser capsulotomy, vitreous densifications, intraretinal hemorrhages, cotton wool spots, and venous dilatation and tortuosity in the inferior arcade were observed, along with peripheric arterial narrowing (Figure 1A), suggesting the presence of previous and simultaneous arterial and venous occlusion. Vitreous densifications in the OD precluded optic disk visualization. In the OS, the optic disk was normal, but hemorrhages along the vascular arcades and cotton wool spots were evident (Figure 1B).

Spectral domain optical coherence tomography (SD-OCT) macular scans of the OD revealed hyperreflectivity and increased thickness of the internal retinal layers as well as poor definition of the external layers and loss of the interdigitation and photoreceptor bands in the foveal region. On the OS, there were hyperreflective round lesions in the inner nuclear layers near the papillomacular bundle, which corresponded to the cotton wool spots seen in fundoscopy. Optic disk–centered SD-OCT scans showed a mean retinal nerve fiber layer (RNFL) thickness of 149 μm on the OS, while low-quality OD optic disk–centered scans precluded RNFL thickness measurements. Fluorescein angiography (FA) and indocyanine green angiography (ICG) revealed a hyperfluorescent optic disk in the early phases; vascular impregnation and some vessel leakage around the vascular arcades in the late phases; as well as peripheral nasal and temporal retinal and choroidal ischemia in the patient's OD (Figure 1A). OS FA and ICG revealed a hyperfluorescent optic disk in the early phases, hypofluorescent round areas around the optic disk (which corresponded to the fundoscopic cotton wool spots), and some confluent retinal ischemia in the extreme temporal periphery (Figure 1B).

A complete diagnostic workup was performed, for possible infectious, inflammatory, and ischemic causes. The patient presented anemia (hemoglobin 11.2 g/dL, normal range 13–18) and an elevation in inflammatory parameters (erythrocyte sedimentation rate of 91 mm/1st hour (ESR, normal range 0–20) and C-reactive protein 70.9 mg/mL (CRP, normal range $<$3.0)). Serum protein electrophoresis revealed a monoclonal gammopathy. No other changes in hemogram, renal, or hepatic function were detected. Infectious causes, including tuberculosis, cytomegalovirus (CMV), type 1 and 2 herpes simplex virus (HSV), varicella-zoster virus (VZV), toxoplasmosis, syphilis, B and C hepatitis, and human immunodeficient virus (HIV), were all excluded. Cerebral magnetic resonance imaging (MRI) revealed signs of ischemic leukoencephalopathy, but no evidence of inflammatory demyelinating lesions or acute ischemic vascular lesions. Carotid and vertebral Doppler ultrasound revealed no stenosis or flux pathological variations.

Given the aforementioned ophthalmic findings (vitreous densifications, retinal hemorrhages, and severe peripheral ischemia with concurrent venous and arterial retinal occlusion) and associated systemic manifestations (such as anemia, monoclonal serum gamma peak, and elevation of inflammatory markers), lymphoproliferative and myelodysplastic conditions, hyperviscosity syndromes, and systemic inflammatory diseases were considered as possible etiologies.

The patient initiated OD retinal panphotocoagulation combined with intravitreal bevacizumab and OS focal retinal photocoagulation

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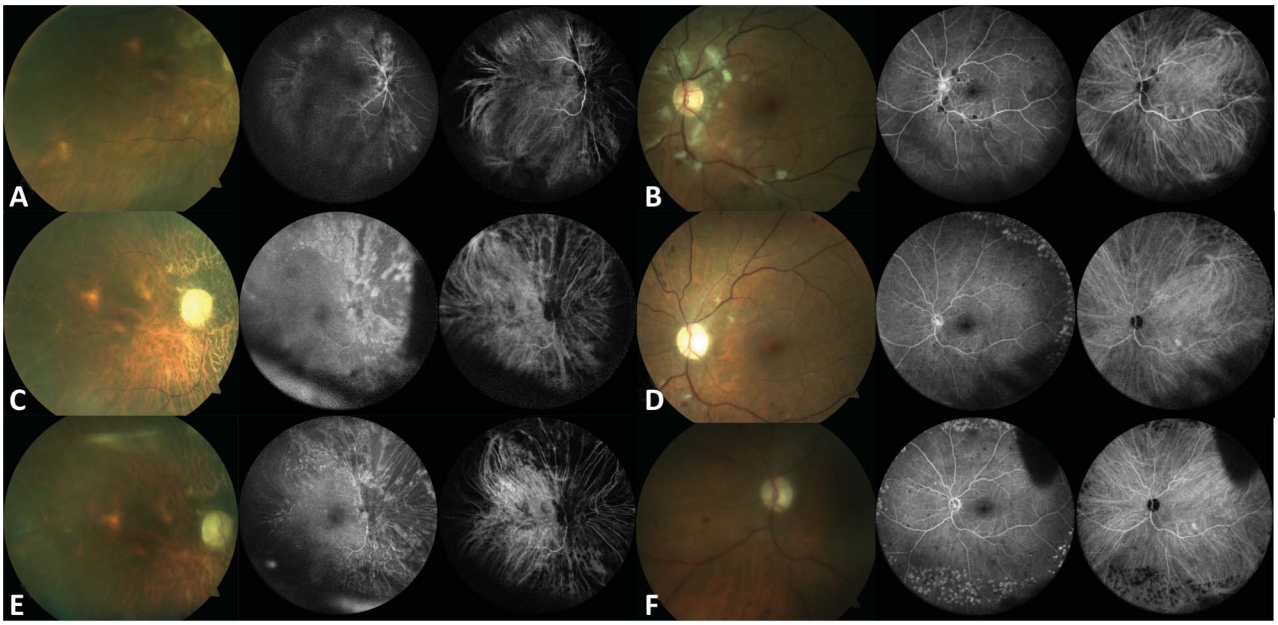

Fig. 1. Follow-up retinographies and fluorescein (FA) and indocyanine green (ICG) angiographic images. Evaluation of the right eye (OD) at presentation (**A**). Fundus image evidenced cotton wool spots and retinal hemorrhages mostly located around vascular arcades. Vitreous densifications in the OD precluded optic disk visualization. Although not shown in the figure, venous dilatation and tortuosity in the inferior vascular arcade, with peripheric arterial narrowing, were evident at presentation. OD FA and ICG revealed a hyperfluorescent optic disk in the early phases and vascular impregnation and leakage in the late phases, as well as with peripheral nasal and temporal retinal and choroidal ischemia. At presentation, the left eye (OS) (**B**) optic disk was normal, but hemorrhages along the vascular arcades and cotton wool spots were evident. OS FA and ICG revealed a hyperfluorescent optic disk in the early phases, hypofluorescent round areas around the optic disk (which corresponded to cotton wool spots observed in the fundoscopy), and some confluent retinal ischemia in the extreme temporal periphery. OD fundus image 2 months (**C**) and 3 months (**E**) after presentation. One month after corticotherapy initiation, vitreous densifications improved, evidencing optic disk pallor and vessel narrowing. On OD FA and ICG angiograms, a progressive enlargement of retinal and choroidal ischemia was observed. OS fundus image 2 months (**D**) and 3 months (**F**) after presentation. Persistent retinal hemorrhages and progressive optic disk pallor were observed in the OS (**B**). Retinal photocoagulation spots are visible in the periphery where laser was performed to treat ischemic areas.

in the ischemic regions. In addition, systemic prednisolone was initiated at a dose of 1 mg/kg/day.

Meanwhile, immunofixation and the remaining hematologic study ruled out lymphoproliferative and myelodysplastic disorders.

After the initiation of systemic corticotherapy, OD vitreous densifications improved gradually, allowing visualization of a pale optic disk, progressive vascular narrowing, and the persistence of retinal hemorrhages and peripapillary cotton wool spots (Figure 1C and E). Despite vitreous densifications' improvement, the OD BCVA dropped to light perception. Moreover, an OS de novo progressive pallor of the optic disk was noted (Figure 1D), associated with progressive VA deterioration from 20/25 to 20/100 in 4 weeks. Follow-up SD-OCT macula and optic disk scans revealed progressive bilateral macular and peripapillary RNFL thickness reduction.

Sequential FA and ICG revealed bilateral enlargement of the retinal and choroidal ischemic areas (Figure 1E and F). During this period, the patient reported an improvement in asthenia after the initiation of corticotherapy. Therefore, considering the presence of systemic symptoms and subsequent improvement with corticotherapy, as well as severe bilateral visual loss with disk pallor and severe retinal and choroid ischemia, and concurrently elevated inflammatory markers, GCA and other vasculitis were considered as likely diagnostic hypotheses, especially after other inflammatory or infectious causes were ruled out.

The patient was immediately referred to Neurology. Doppler ultrasound revealed hypoechogenic halos on all arterial wall segments of the superficial temporal arteries, which confirmed the diagnosis of GCA.

After systemic corticotherapy initiation, the patient's asthenia significantly improved, while anemia resolved and inflammatory markers decreased (follow-up ESR of 26 mm/1st hour and CRP of 28 mg/mL). BCVA stabilized in counting fingers on the OS, although the OD BCVA became no light perception. One year after presentation, the patient is still receiving oral corticotherapy with very slow tapering and is being followed in Ophthalmology, Neurology, and Internal Medicine consultations. Besides severe bilateral low vision, no other systemic sequelae developed during follow-up.

Discussion

GCA constitutes the most common vasculitis in adults, posing a significant risk of vision loss if not timely managed. The variability of symptoms, as well as their nonspecificity, can sometimes result in an incorrect diagnosis, delaying treatment. We present a case of GCA with an unusual presentation, highlighting the importance of being aware of atypical clinical presentations and the importance of having a high clinical suspicion in these situations.

Our patient presented with bilateral visual loss and a complex ophthalmic presentation that masked the diagnosis. The presence of bilateral cotton wool spots, retinal hemorrhages, and retinal and choroidal ischemia led to different diagnostic hypotheses. Furthermore, the severe ischemia in the OD and ophthalmic history (with previous retinal hemorrhages and cystoid macular edema and possible uveitis), as well as the analytic monoclonal gamma peak, favored other diagnoses over GCA. In addition, vitreous densifications prevented visualization of the pallor of the OD optic disk, which would have been relevant to the final diagnosis.

Although the inflammatory and ischemic signs present in our case are more frequently associated with other diagnoses that must be excluded first, GCA should not be overlooked. Indeed, although rare, the presence of uveitis or isolated ocular ischemia can constitute the first ophthalmic signs of GCA.[4–6]

Védrine et al[7] emphasized the occurrence of uveitis as a presenting feature of GCA. The authors consider that uveitis occurs due to ischemia of the posterior ciliary arteries, presenting with anterior, posterior, or panuveitis. According to the authors, posterior uveitis typically appears as choroidal ischemic lesions that progress to peripheral chorioretinal degenerative patches, while anterior uveitis, caused by anterior segment ischemia, manifests as keratic precipitates and cells in the anterior chamber. Given the ischemic component, a relative afferent pupillary defect is expectable. Some reports of uveitis as a GCA presenting sign exist in the literature, ranging from anterior[4] to posterior uveitis[8,9] or panuveitis.[6,10]

Similarly, GCA can also present with progressive and indolent ocular ischemia. However, not many case reports in the literature[5,11,12] describe cotton wool spots as the first sign of the disease.

Despite the rarity of these descriptions, GCA pathophysiology is based on an inflammatory response to the arterial wall, resulting in ischemia. As a result, all potential consequences of these vascular inflammatory reactions can constitute a disease presentation. The awareness of these atypical manifestations is critical to the diagnostic workup and might contribute to a better appreciation of other ophthalmic or systemic signs that might have been overlooked.

To establish GCA diagnosis as early as possible, the patient's signs and symptoms should be interpreted considering certain laboratory studies, including ESR, CRP, and platelet count.[13,14] In our case, ESR and CRP were both elevated since the beginning. Because these are acute phase proteins that are also elevated in anemia and several other inflammatory disorders, including malignancies and hematologic diseases, their upregulation was interpreted as a possible sign of the aforementioned diagnostic hypotheses, not considering GCA as our primary diagnostic hypothesis.

After bilateral VA deterioration and the exclusion of hematologic causes, the diagnostic hypotheses were reviewed. Vitreous densification resolution allowed higher quality angiographic images, showing severe retinal and choroidal ischemia. The multiple changes observed in multimodal retinal imaging, their evolution over time, together with the persistent elevation of serum inflammatory markers, significantly favored the diagnosis of GCA, which was subsequently confirmed by temporal artery Doppler ultrasound. Biopsy was long thought to be necessary for GCA diagnosis. However, in centers with appropriate training and expertise, Doppler ultrasound is considered sufficient.[15,16]

If GCA had been suspected during the initial evaluation, inflammatory serum markers would have been valued and a temporal artery ultrasound and diagnosis would have been performed sooner. This would be beneficial because high-dose corticotherapy should be started as soon as possible in GCA.[1,3] Although no optimal regimen has been defined due to conflicting results and low-quality evidence,[3] it is consensual to perform IV pulses of methylprednisolone at diagnosis especially when there is a threat to vision.[1,16]

Despite the delay in diagnosis in our case, high-dose oral corticotherapy (prednisolone 1 mg/kg/day) was started immediately after infectious causes were ruled out. However, no methylprednisolone pulses were administered because they were considered of limited utility by the time the GCA diagnosis was established, considering the presence of bilateral ophthalmic involvement, with severely decreased VA and irreversible optic disk atrophy. Furthermore, systemic symptoms resolved with high-dose oral corticotherapy. Nevertheless, even with effective medical therapy, reports of permanent partial or complete vision loss range from 8.2% to 20%.[17,18]

Our case highlights the importance of a high GCA clinical suspicion in cases of significant ocular ischemia, especially in older patients, given the potential severity of this vasculitis. Similarly, uveitis may also be considered a sign of GCA in high-risk patients. This report is also notable for the significant time lag between the patient's potential first anterior uveitis and the current presentation with severe ocular ischemia and optic neuritis. This slow progression over time may represent the natural history of disease when left untreated. Furthermore, this case also emphasizes the importance of a scrupulous medical history, even in patients who already present a systemic follow-up by

other medical specialties. Despite the treatment delay and the final severe visual outcome, the diagnosis was made before more serious systemic complications developed, such as stroke, heart attack, or aortic aneurysm rupture.

In conclusion, GCA is a threatening condition for which prompt diagnosis and treatment are critical for a better prognosis. GCA often presents with vision loss, and ophthalmologists are on the frontline of its diagnostic process. Given the wide spectrum of presentations, physicians must be familiar with both typical and atypical presentations. A high index of suspicion, combined with a regular and structured follow-up, extensive investigation, and teamwork assessment, is critical for a correct and timely diagnosis, preventing further complications and a poor ophthalmic and systemic prognosis.

Key words: choroidal ischemia, giant cell arteritis, large vessel vasculitis, optic neuropathy, retinal ischemia.

References

1. Lyons HS, Quick V, Sinclair AJ, et al. A new era for giant cell arteritis. Eye (Lond) 2020;34:1013–1026.
2. Larsson K, Mellström D, Nordborg E, et al. Early menopause, low body mass index, and smoking are independent risk factors for developing giant cell arteritis. Ann Rheum Dis 2006;65:529–532.
3. Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia rheumatica and giant cell arteritis: a systematic review. Jama 2016;315:2442–2458.
4. Bandini F, Benedetti L, Ceppa P, Corallo G. Uveitis as a presenting sign of giant cell arteritis. J Neurophthalmol 2005;25:247–248.
5. Daudin JB, Bluwol E, Chaine G, Rohart C. [Cotton-wool spots as first ocular manifestation of giant cell arteritis]. J Fr Ophtalmol 2006;29:e28.
6. Rajesh CV, Cole M. Panuveitis as a presenting feature of giant cell arteritis. Br J Ophthalmol 2000;84:337d.
7. Védrine L, Algayres JP, Coutant G. Giant-cell arteritis. N Engl J Med 2003;348:1497–1498.
8. Nguyen NV, Karkhur S, Yuksel M, et al. Posterior uveitis associated with large vessel giant cell arteritis. Ocul Immunol Inflamm 2022;30:2019–2022.
9. Slemp SN, Martin SE, Burgett RA, Hattab EM. Giant cell arteritis presenting with uveitis. Ocul Immunol Inflamm 2014;22:391–393.
10. Dasgupta B, Pitzalis C, Panayi GS. Inflammation of the uveal tract as a presenting feature of temporal arteritis. Ann Rheum Dis 1989;48:964–965.
11. Asensio Sánchez VM, Pegalajar Maeso M, Rodríguez Bravo I, Carrasco E. [Cotton-wool spots as the first manifestation of giant cell arteritis: two cases]. Arch Soc Esp Oftalmol 2004;79:449–451.
12. Johnson MC, Lee AG. Giant cell arteritis presenting with cotton wool spots. Semin Ophthalmol 2008;23:141–142.
13. Rahman W, Rahman FZ. Giant cell (temporal) arteritis: an overview and update. Surv Ophthalmol 2005;50:415–428.
14. Hazleman B. Laboratory investigations useful in the evaluation of polymyalgia rheumatica (PMR) and giant cell arteritis (GCA). Clin Exp Rheumatol 2000;18:S29–S31.
15. Maz M, Chung SA, Abril A, et al. 2021 American college of rheumatology/vasculitis foundation guideline for the management of giant cell arteritis and takayasu arteritis. Arthritis Rheumatol 2021;73:1349–1365.
16. Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79:19–30.
17. Hayreh SS, Zimmerman B. Visual deterioration in giant cell arteritis patients while on high doses of corticosteroid therapy. Ophthalmology 2003;110:1204–1215.
18. Chen JJ, Leavitt JA, Fang C, et al. Evaluating the incidence of arteritic ischemic optic neuropathy and other causes of vision loss from giant cell arteritis. Ophthalmology 2016;123:1999–2003.