Case Reports in Neurology

Case Rep Neurol 2022;14:483–490
DOI: 10.1159/000527876
Received: July 26, 2022
Accepted: October 26, 2022
Published online: December 5, 2022

Single Case – General Neurology

Ischemic Optic Neuropathy Secondary to Varicella-Zoster Vasculitis Mimicking Giant Cell Arteritis: Case Report

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Keywords
Vasculitis · Giant cell arteritis · Ischemic optic neuropathy · Varicella zoster virus · Encephalitis · Case report

Abstract
Differentiating GCA from its many mimickers remains a challenge in the daily clinical practice, especially in patients presenting with unspecific manifestations. We present the case of an 82-year-old woman who presented with a 3-week history of left eye vision loss secondary to bilateral edema and hemorrhage of the optic discs. Despite negative bilateral temporal artery biopsies, the elevation of the inflammatory markers and brain MRA findings suggestive of temporal arteritis as well as stenosis of the basilar artery led us to initiate treatment with high-dose steroids. Inflammatory markers remained elevated despite high-dose steroids which prompted additional work leading to a diagnosis of varicella-zoster encephalitis. Steroid treatment was quickly tapered off and treatment with acyclovir resulted in the normalization of the acute phase reactants. The persistence of elevated inflammatory markers despite high-dose steroids should prompt additional work up for the search of an alternative diagnosis of GCA mimickers.

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Introduction

Giant cell arteritis (GCA) is the most frequent type of primary systemic vasculitis in the USA and Europe. It characteristically affects people older than 50 and has a wide variety of clinical manifestations, including headache, scalp tenderness, jaw or tongue pain or claudication, fever, night sweats, fatigue, malaise, weight loss, and polymyalgia rheumatica, among others, many of which, are unspecific. The most feared manifestation is visual loss, which is rarely reversible. The inflammatory markers are usually, elevated [1]. The temporal artery biopsy (TAB) is still considered the gold standard for diagnosis, and although a negative biopsy does not rule out the diagnosis, a positive artery biopsy is diagnostic in most cases.

In the past few decades, noninvasive imaging studies, particularly color Doppler ultrasonography but also magnetic resonance angiogram (MRA), have been proposed to substitute the need for an invasive procedure, but this approach has not achieved universal acceptance yet [2]. Many other disorders may mimic GCA, including malignancy, and infections [2], as well as other noninfectious and nonmalignant conditions [3, 4]. Establishing a firm diagnosis whenever possible, prior to initiating treatment with immunosuppression, is crucial as many of the mimics may be masked or worsened by immunosuppression. We report the case of a patient who presented with clinical features and imaging findings suggestive of GCA, although with negative bilateral TABs and was ultimately diagnosed with infectious vasculitis.

Case Presentation

An 82-year-old woman presented with a 3-week history of left eye vision loss. The patient came to our institution's ophthalmology clinic for her annual eye exam.

During that visit, she mentioned to her optometrist that 3 weeks prior, while watching TV she had noticed sudden onset of a blind spot in her left eye, which since the onset had persisted and remained stable. The optometrist found that the patient had bilateral optic disc edema and peripapillary hemorrhages raising concerns for, GCA. Neurology was consulted and recommended direct hospital admission.

Her past medical history was relevant for cataracts, multifocal atrial tachycardia, diverticulosis, multiple skin cancers, including melanoma status postsurgical excision over 30 years ago, peptic ulcer disease, stage 3 chronic kidney disease, bilateral hearing loss, lower extremity edema, viral epiglottitis complicated by sepsis, pneumonia and respiratory failure, rectal sigmoid perforation and peritonitis requiring colostomy, and a right distal radius fracture. Regarding her social history, the patient was married and had three children. She was working part-time at a local elementary school and daycare. She had never smoked, used illicit drugs, or consumed alcohol. Her family history was remarkable for cancer in several relatives, especially skin cancer including melanoma, ischemic attack in her daughter, diabetes mellitus in her mother, and lung cancer in her father.

On admission, she was evaluated by neurology and rheumatology. The central blind spot in her left eye had caused her to be unsteady on her feet and had resulted in several falls. She had not hit her head or lost her consciousness. For the past 7 days, she had had symptoms of an upper respiratory infection with cough, runny nose, and congestion. She had not had any recent onset of a new type of headache, eye pain, double vision, blurry vision, floaters, or flashing lights. She had not had fever, night sweats, weight loss, jaw pain/claudication, or scalp tenderness. She had had no cough or shortness of breath. All other review of systems was negative.

Her physical exam was remarkable for temperature of 37°C, heart rate 83 bpm, respiratory rate 20 breaths per minute, blood pressure 111/81, O2 saturation: 93% on room air. She was in no acute distress and was alert and oriented in person, place, and time. She had no scalp

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tenderness. She had no thickening or tenderness over her temporal arteries and the temporal pulses were present and symmetric. Her cardiac and lung auscultation were unremarkable. Her abdomen was soft, nontender, nondistended, and she had an ostomy with soft-formed stool output. She had 1 + pitting edema in lower extremities, and her radial and dorsalis pedis pulses were present and symmetric. She had bony hypertrophy in the proximal and distal interphalangeal joints of both hands without signs of synovitis. Range of motion was normal in all joints of the upper and lower extremities. Cranial nerves III through XII were intact. Her strength was 5/5 proximal and distal in the upper and lower extremities. Coordination and gait were normal. Her sensation was grossly intact. She reported a central visual field defect in the left eye.

Her laboratories revealed hemoglobin: 11.3 g/dL, white blood cell count: 6.6 × 109/L with normal differential, platelets: 183 × 103/L, erythrocyte sedimentation rate (ESR): 42 mm/h, prothrombin time: 12.1 s, INR: 1, Na: 140 mmol/L, K: 4.3 mmol/L, Cl: 102 mmol/L, bicarbonate: 28 mmol/L, anion GAP: 10, BUN: 25.3 mg/dL, creatinine: 1.05 mg/dL, eGFR: 50 mL/min, calcium: 9 mg/dL, glucose: 86 mg/dL, bilirubin total: 0.3 mg/dL, bilirubin direct<022 mg/dL, alanine aminotransferase: 10 U/L, aspartate aminotransferase: 19 U/L, alkaline phosphatase: 69 U/L, protein total: 7.2 g/dL, albumin 4.1 g/dL, C-reactive protein (CRP): 16.1 mg/L. Rheumatoid factor, antinuclear antibody, anti-dsDNA, anti-Ro, anti-La, anti-Sm, anti-RNP, anti-Scl 70, anti-Jo 1, anti-myeloperoxidase, and anti-proteinase 3 antibodies: all negative. C3: 69 (21–50) U/mL, C4: 32 (14–40) U/mL.

An electrocardiogram revealed normal sinus rhythm without repolarization abnormalities. A chest X-ray showed mild cardiomegaly with tortuosity thoracic aorta, without consolidation, pleural effusion, or pneumothorax and without evidence of tuberculosis. A chest computerized tomography angiogram revealed no findings suggestive of vasculitis in the thorax and a 4-centimeters stable aneurysmal dilation of the ascending aorta without any acute aortic abnormality. A 9–10 mm irregular nodules in the left lower lobe were indeterminate. Resolution of pleural effusions and near resolution of pericardial effusion and bibasilar airspace opacities was observed. A brain magnetic resonance imaging (MRI) with and without contrast showed no acute intracranial abnormality, an 8-mL left frontal meningioma, moderate small vessel ischemic change and sinusitis. An MRI of the orbits revealed no definite orbital abnormality, prominent vessels in the right greater that left temporal scalp, which was suggestive of temporal arteritis. A neck MRA revealed normal appearance of the cervical carotid and vertebral arteries without stenosis or dissection. A brain MRA revealed a long segment mild-to-moderate stenosis of the proximal basilar artery, and mild asymmetric narrowing of the left middle cerebral artery M2 branches (Fig. 1), which was more clearly seen in the 3-D reconstructed images (Fig. 2).

Bilateral temporal artery biopsies were performed which revealed arteriosclerosis with focal calcifications and no significant acute or chronic inflammation. Overall, the presentation in an elderly patient of bilateral optic disc edema, peripapillary hemorrhages, elevated inflammatory markers, and negative bilateral TABs continued to be concerning for GCA. However, consideration of other entities was broad and our differential diagnosis included, but was not limited to, nonarteritic ischemic optic neuritis, tumor, demyelinating disease, elevated intracranial pressure due to thrombosis of the cerebral vein and/or sinuses, infectious, other vasculitides, or paraneoplastic. A transthoracic echocardiogram was performed and was unremarkable demonstrating no changes from prior studies. Lumbar puncture was not initially performed.

She received IV methylprednisolone 1 g daily for 3 days. She was then transitioned to oral prednisone at the dose of 60 mg (mg) po daily until follow-up in rheumatology clinic in 3–4 weeks. Aspirin 81 mg po daily, atovaquone, and calcium, and vitamin D supplementation were also prescribed. There was a plan to discuss initiation of tocilizumab during her subsequent follow-up visit in the clinic.

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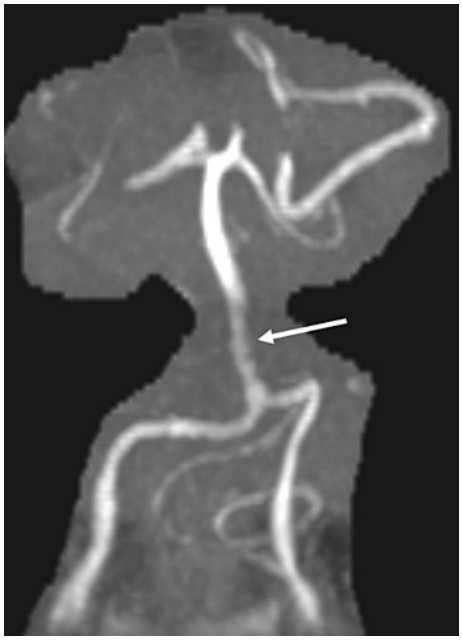

Fig. 1. Intracranial MRA demonstrates a moderate length segment of smooth narrowing of the proximal basilar artery (arrow).

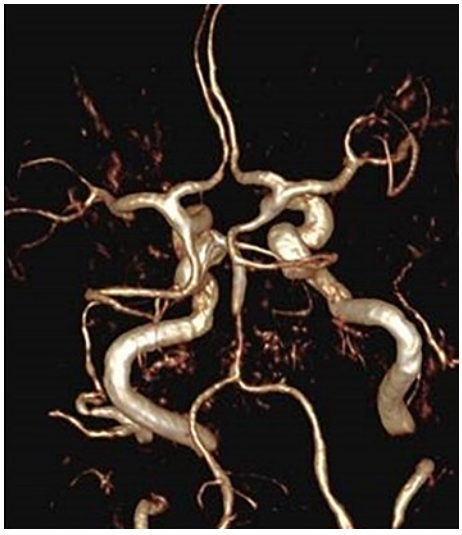

Fig. 2. Tridimensional reconstruction of the initial intracranial MRA demonstrating the narrowing of the proximal basilar artery.

One-week post after hospital discharge, she was evaluated in the neuro-ophthalmology clinic. Neuro-ophthalmic examination revealed a distance-corrected visual acuity of 20/40 -2 in the right eye and CF 2′ in the left eye. Near corrected visual acuity was 20/25 in the right eye and 20/800- in the left eye. The pupillary examination demonstrated a 0.9 log unit left relative afferent pupillary defect. The patient was able to identify all the Ishihara color plates in the right eye and none in the left eye. Depth perception vision by stereo acuity Titmus testing was 800 s of arc. The ocular motility examination revealed full ocular ductions in each eye with no evidence of misalignment or nystagmus. Slit lamp biomicroscopic examination of the anterior segment was significant for bilateral nuclear sclerotic lenticular changes. Zeiss Central 30-2 SITA Humphrey visual field testing revealed a paracentral defect in the right eye and a dense superior altitudinal defect in the left eye. Funduscopic examination demonstrated

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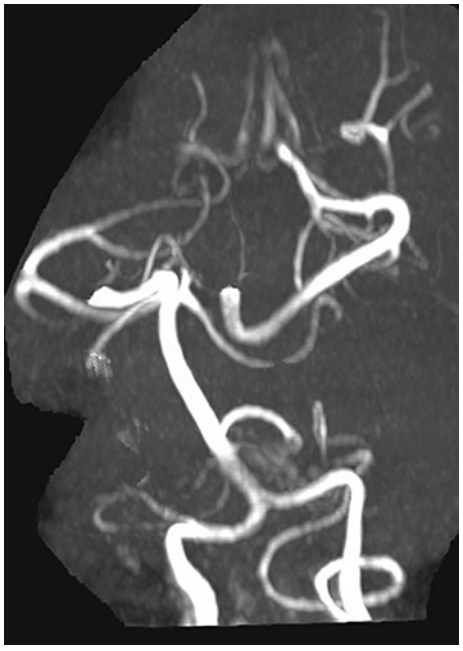

Fig. 3. Follow-up intracranial MRA 2 months later demonstrates resolution of the narrowing with normal appearance of the basilar artery.

right optic disc edema with peripapillary hemorrhages and left pallid optic disc edema with peripapillary hemorrhages.

Despite high-dose steroid treatment for days, the CRP and ESR remained elevated. At this time, cerebrospinal fluid (CSF) analysis with opening pressure was recommended to rule out inflammatory, autoimmune, and infectious etiologies. The lumbar puncture revealed normal opening pressure, without accompanying or elevation in CSF protein. The CSF polymerase chain reaction was positive for varicella zoster virus (VZV). The patient had a prior history of chickenpox in her early teenage years and zoster as an adult 14 years ago; she had had the shingle vaccine.

The patient was finally diagnosed with bilateral arteritic ischemic optic neuropathies secondary to VZV infection. IV acyclovir was started, and she received 14-day home infusions through a PICC line, and the prednisone dose was decreased to 50 mg PO daily. After 2 weeks of IV acyclovir, the rheumatologic evaluation revealed normalization of the inflammatory markers, and she was started on a rapid oral prednisone taper. Two months post visual loss onset, a brain MRA was repeated that showed improvement in the basilar artery stenosis (Fig. 3). In follow-up visits, the patient had stable visual acuity in each eye and bilateral optic disc atrophy. She had no systemic GCA symptoms including headache, jaw claudication, scalp/temporal tenderness, or symptoms suggestive of polymyalgia rheumatica. One-year post-onset, her inflammatory markers have remained stable.

Discussion

We report the case of a patient presenting with sudden onset of vision loss due to VZV vasculitis. The initial clinical history and findings mimicked features of vasculitis and she was initially mistakenly diagnosed with GCA.

The possible infectious etiology of vasculitis has been debated for decades [5]. VZV can produce vasculopathy both in intracranial and extracranial arteries [6, 7]. In addition to ischemic and hemorrhagic strokes, cerebral sinus thrombosis is associated with central nervous system VZV infection [8, 9]. There is still controversy regarding whether VZV is a

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possible causal agent of GCA. Several investigators, including us, did not find DNA of VZV. in either positive or negative biopsies for GCA [10, 11]. In contrast, other authors have reported VZV in some temporal arteries with GCA [12]. Other authors found it in both positive and negative TABs and concluded that this suggested the possible role of VZV in triggering the immunopathology of GCA [7]. Multifocal VZV vasculopathy can cause sudden vision loss through ischemic optic neuropathy, and elevated ESR and/or CRP levels, even in patients without zoster history and/or acute herpetic rash. This may prompt the clinician to believe that the ischemic optic neuropathy is due to GCA. A positive TAB is very helpful to diagnose GCA; however, when the TABs are negative, the physician must formulate a management plan based on the clinical findings. The failure of acute phase reactants to respond to high-dose steroids and devastating bilateral visual loss prompted testing revealing a viral infection. The antiviral therapy stabilized the inflammatory markers and vision as in previously reported cases [13–17].

Despite the advances in noninvasive imaging studies, a biopsy can be immensely helpful, primarily for the diagnosis of GCA if it is positive, and also to rule out other diseases such as infection, malignancy or thrombosis. The lack of evidence of temporal artery abnormalities, scalp tenderness, or jaw claudication significantly decreases the likelihood of a positive TAB for GCA [1], and our patient did not have any of those symptoms.

Establishing a firm diagnosis whenever possible, prior to initiating treatment with immunosuppression, is key as many of the mimics may be masked or worsened by immunosuppression. In the case of our patient, the lack of other cranial symptoms characteristic of GCA in addition to persistently elevated inflammatory markers despite high-dose steroids led us to pursue further investigations before adding additional immunosuppressive treatment.

In conclusion, careful consideration and diagnostic investigation should be warranted in a subgroup of patients with ischemic optic neuropathy, especially when they do not present with other cranial symptoms suggestive of GCA to enhance recognition and treatment of uncommon VZV vasculitis.

Our paper highlights that differentiating GCA from its many mimickers remains a challenge in the daily clinical practice, that imaging studies are helpful for the diagnosis of GCA but the TAB, even if it is negative, continues having an important role, and that the persistence of elevated inflammatory markers despite high-dose steroids, should prompt additional work up for the search of an alternative diagnosis of GCA mimickers. The CARE Checklist has been completed by the authors for this case report, attached as for all online suppl. material, see www.karger.com/doi/10.1159/000527876.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

Alicia Rodriguez-Pla, Marie F. Grill, Geoffrey P. Fletcher, and Marie A. Di Nome have no financial disclosures.

Funding Sources

No funding or grant support was provided for this manuscript.

Author Contributions

Alicia Rodriguez-Pla: substantial contribution to the conception or design of the work, acquisition, and interpretation of the data for the work, drafting the manuscript, revise it critically for important intellectual content; final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Marie F. Grill: substantial contribution to the interpretation of data for the work, and revise the draft critically for important intellectual contents, and final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Geoffrey P. Fletcher: substantial contribution to the interpretation of data for the work, and revise the draft critically for important intellectual contents, and final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Marie A. Di Nome: substantial contribution to the interpretation of data for the work, and revise the draft critically for important intellectual contents, and final approval of the version to be published and agree to be accountable for all aspects of the work are appropriately investigated and resolved.

Data Availability Statement

All data that support the findings of this study are included in this article.

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