Case Report

**Orbital Apex Syndrome, Intracranial & Dural Involvement in Giant Cell Arteritis (GCA)**

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Received: 30 August 2019 / Accepted: 23 September 2019

**Abstract**

Orbital apex syndrome and posterior ischaemic optic neuropathy are rare presentations of GCA and are clinically characterized by complex ophthalmoplegia with 2nd, 3rd, 4th, 5th (ophthalmic division) and 6th cranial nerve palsies. More than 80% of visual loss in GCA are due to arteritic anterior optic ischaemic neuropathy (A-AION) with clinical evidence of optic disc swelling. A major pitfall in diagnosis is the presence of a normal optic disc despite visual loss, albeit rare, can be due to posterior ischaemic optic neuropathy (PION) or cortical infarct involving calcarine cortices and requires a high index of clinical suspicion. GCA predominantly affects cranial and extracranial vessels with elastic membranes.

On the contrary, true intracranial vessel and dural involvement in GCA are exceedingly rare and are not well documented, as the vessels are devoid of elastic membranes upon entering the dura. Intracranial involvement may result in altered sensorium, localizing signs, speech and memory deficits. Neuroimaging may show multifocal dural thickening and enhancement, which can resolve with treatment.

We describe a 62 year old male patient with underlying diabetes mellitus, end stage renal disease on hemodialysis and hypertension, presenting with new onset headache, jaw claudication, bilateral complex ophthalmoplegia and posterior ischaemic optic neuropathy. He was diagnosed with GCA with bilateral orbital apex syndrome. He had fluctuating level of consciousness, became comatose and was intubated for cerebral protection. Unfortunately, his condition deteriorated rapidly and he succumbed. His mental deterioration was attributed to intracranial vessel and dural involvement. This case highlights the atypical and rare manifestation of GCA.

**Keywords:** Giant Cell Arteritis, GCA, Orbital Apex Syndrome, Vasculitis, Optic neuropathy, dural, intracranial

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DOI: 10.5455/ww.63501

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Introduction:

Giant cell arteritis (GCA) is the most common type of vasculitis in patients above the age of 50. Visual loss is a feared complication of GCA, and requires prompt diagnosis. Orbital apex syndrome and posterior ischaemic optic neuropathy are rare presentations of GCA and are clinically characterized by complex ophthalmoplegia with 2nd, 3rd, 4th, 5th (ophthalmic division) and 6th cranial nerve palsies.

True intracranial vessel and dural involvement in GCA are exceedingly rare and are not well documented. We describe a 62 year old gentleman presenting with new onset headache, complex ophthalmoplegia and visual loss with normal optic discs. He was diagnosed as GCA with bilateral orbital apex syndrome and posterior ischaemic optic neuropathy. He subsequently developed altered sensorium as a sequelae of intracranial vessel and dural involvement. This case highlights the intricate and rare manifestation of GCA.

Case

A 62 year old gentleman of malay descent presented with history of progressive blurring of vision and binocular diplopia for 2 months duration. He was premorbidly independent and had underlying diabetes mellitus, hypertension and end stage renal disease on regular hemodialysis via left internal jugular vein cuffed catheter for the past 10 years following failed fistula creation.

He was initially seen by the ophthalmologist, and had isolated reduced visual acuity of 6/45 bilaterally with normal extraocular muscle movement range. Otherwise, bilateral fundi, optic discs, intraocular pressure, cornea, conjunctivae and all cranial nerves were normal. Contrasted computed tomography of brain and orbits were normal. He was discharged with appointment to reassess his condition.

A month later, he experienced worsening of vision and presented to the emergency department. Unfortunately, he was found to have bilateral eye total blindness with no perception of light bilaterally. However, once again, his fundi, optic discs were normal without evidence of retinopathy. He had new bilateral cranial nerve palsies, involving 2nd, 3rd, 4th, 6th and V1 division of 5th cranial nerves with clinical signs of bilateral ptosis worse over left, complete ophthalmoplegia with restricted gaze over all directions and reduced sensation over V1 division of trigeminal nerves bilaterally. Pupils were 4mm and nonreactive.

A medical consult was obtained. On further history, he complained of new onset of headache for the past 9 months, preceding the onset of visual symptoms by 6 months. He described the headache as throbbing over bilateral temporal regions; left worse than right side. He had been experiencing jaw claudication for 9 months as well. Otherwise, no history of limb claudication, fever, weight loss, night sweats, syncope, vomiting, seizures or limb weakness. No features of polymyalgia rheumatica.

His GCS was full, normotensive with blood pressure of 129/80, pulse 89 beats per minute, oxygen saturation 99% on room air, capillary glucose 8.9 and afebrile.

He had prominent thickened, tender, nodular temporal arteries with diminished pulsation bilaterally worse over the left side (Figure 1). He had no vascular bruit. He had no limb motor weakness, normal sensory testing, normal cerebellar and gait testing. No meningism. His reflexes were normal with flexor plantar response for Babinski.

His other cranial nerves were intact. Respiratory, cardiovascular and abdominal systems examination were unremarkable. ECG and chest radiograph were normal.

Based on neuroanatomy localization, involved cranial nerve palsies were consistent of orbital apex syndrome; left worse than right side.

Repeated contrasted computed tomography of brain and orbits showed new enhanced thickening of dura adjacent to cavernous sinus bilaterally with extension to the orbital apex, superior orbital fissure and temporo-frontal region, more over the left side. Both optic nerves were prominent with diameters measuring 6.1mm over the right and
6.6mm over the left side. No abnormal enhancement seen over optic nerves. There were no other abnormalities or thrombosis. Radiological features were suggestive of inflammatory disease. However, we did not proceed with magnetic resonance imaging for him.

His blood investigation showed raised inflammatory markers with c-reactive protein of 110mg/L (normal <5) and erythrocyte sedimentation rate of 98mm/h. Other results include white cell count of 6000, normochromic normocytic anaemia with haemoglobin of 6gm/L, platelets 193000, haematocrit 46, urea 10mmol/L, sodium 132mmol/L, potassium 5mmol/L, creatinine 384 micromol/L, albumin 36g/L, aspartate transaminase 11 U/L, alanine transaminase 12 U/L, alkaline phosphatase 119 U/L and bilirubin 10 micromol/L.

A preliminary diagnosis of orbital apex syndrome secondary to giant cell arteritis was made. He was started on intravenous hydrocortisone 100mg TDS, and his headache remarkably resolved just after 4 doses of steroids. He was not pulsed with high dose intravenous methylprednisolone as he had established total bilateral blindness and he refused for lumbar puncture to exclude intracranial infection.

Temporal artery ultrasonography showed halo sign and non compressible vessels bilaterally suggestive of giant cell arteritis. He was planned for early magnetic resonance angiography as outpatient for evaluation of vessel inflammation and temporal artery biopsy.

He was discharged well with oral prednisolone 60mg daily and azathioprine 50mg daily to facilitate steroid taper due to his underlying diabetes mellitus and comorbidities. However, he presented 1 day later with new altered sensorium. His GCS was E3V2M5 ; 10/15. He did not have any other new neurological deficit on examination. No meningism and afebrile. Repeated computed tomography of brain had no new changes or infarcts. He was initially treated for presumed meningoencephalitis and was started on intravenous ceftriaxone 2gm BD and intravenous acyclovir 500mg TDS. However, lumbar puncture done had normal opening pressure of 22mmHg, clear and colorless. The protein was elevated at 1099mg/L with normal glucose 5.2mmol/L and had pleocytosis 252 \( (x10^6 \text{ cells per Litre}) \); neutrophils 57\% and lymphocytes 43\%.

CSF culture, cytology, bacterial antigens, Indian ink, cryptococcal antigen and CSF viral study (cytomegalovirus / herpes simplex / ebstein barr virus / varicella zoster / enterovirus), tuberculosis PCR were all negative. Blood cultures had no growth.

A diagnosis of altered sensorium secondary to intracranial vessels and dural involvement was made and planned for high dose methylprednisolone pulse. Unfortunately, patient rapidly deteriorated and was intubated for cerebral protection and succumbed.

Discussion:

GCA is a large and medium vessel vasculitis that typically affects patients above the age of 50. Common presentation includes new onset headache, visual symptoms (amaurosis fugax, diplopia, visual loss), constitutional symptoms (fever, weight loss, night sweats), jaw/tongue claudication, limb claudication and associated symptoms of polymyalgia rheumatica. Examination may show thickened, tender temporal arteries with or without reduced pulsation, scalp tenderness, bruit and blood pressure discrepancies between limbs.

Thickened and nodular temporal arteries such as seen in our patient is a classical finding, albeit rare, in patients with GCA and generally suggest a longstanding, undiagnosed disease. The presence of nodular thickening is associated with odds ratio of 4.5 for biopsy proven GCA, hence a good predictor for a positive temporal artery biopsy.

Diplopia is seen in 15% of patients with GCA and is caused by ischaemia of cranial nerves, extraocular muscles (supplied by ophthalmic artery) or brainstem (infacts within vertebral or posterior cerebral arteries territories). Ophthalmic artery gives rise to the vasa nervorum of 3rd, 4th and 6th cranial nerves that are responsible for extraocular muscle movements. Hence involvement of the vasa nervorum can result in cranial nerve palsies and give rise to ophthalmoplegia, such as in the case of our patient.
Visual loss in GCA can be due to various pathogenetic mechanisms including arteritic anterior ischaemic optic neuropathy (A-AION), posterior ischaemic optic neuropathy (PION), central or branch retinal artery occlusion (CRAO or BRAO), ophthalmic artery occlusion and posterior circulation stroke. In 80% of cases, visual loss is due to A-AION and will be characterized by swollen optic disc, that can be seen even after 24 hours. A major pitfall leading to missed diagnosis is the presence of normal optic disc in patients with visual symptoms. Normal optic disc is seen particularly in two main circumstances; posterior circulation stroke involving calcarine cortices, leading to cortical blindness and more importantly in PION. In PION, the ischaemia affects the retrobulbar portion of the optic nerve via the occlusion of the proximal posterior ciliary artery, causing the optic disc to appear normal during the initial period, and subsequent disc atrophy/pallor develops 4 to 6 weeks later. Our patient had normal fundus examination findings despite total blindness, and computed tomography of brain had no evidence of posterior circulation infarcts. This suggests PION as the mechanism of blindness in our patient, and is seen in less than 10% of patients. PION is diagnosed on clinical grounds by excluding other causes for visual loss. A normal fundus examination without clinical suspicion of GCA resulted in missed diagnosis during his initial presentation.

The orbital apex is defined anatomically as the posterior part of the orbit at the craniofacial junction, where the four orbital walls converge.

Orbital apex syndrome is characterized by dysfunction of the 2nd, 3rd, 4th, 6th and ophthalmic division (V1) of the 5th cranial nerves. This can be distinguished from superior orbital fissure syndrome and cavernous sinus syndrome, in which the 2nd cranial nerve is spared. Patients with cavernous sinus syndrome may also have involvement of the maxillary division (V2) of the 5th nerve. Patients will orbital apex syndrome will present with ophthalmoplegia, ptosis, mydriasis, diplopia, restricted movement of extraocular muscles (due to 3rd 4th 6th cranial nerves), visual loss (2nd nerve) and hypeaesthesia or pain over ophthalmic division of 5th nerve.

Common causes for orbital apex syndrome can be inflammatory (sarcoidosis, Churg-Strauss, Wegener’s granulomatosis, Tolosa Hunt syndrome, orbital pseudotumor, giant cell arteritis), infection (bacteria, fungi, tuberculosis, viral), neoplastic, trauma and vascular (carotid cavernous aneurysm, carotid cavernous fistula, cavernous sinus thrombosis).

History of unexplained dry cough not attributable to other etiology can be seen in patients with GCA. Our patient had history of dry cough for 6 months, with no diurnal variation or constitutional symptoms. The exact pathophysiology of dry cough in GCA is complex and is thought to be due to ischaemia affecting cough receptors at the respiratory tract.

GCA predominantly affects the cranial (extradural vessels) and to a lesser extent extracranial vessels involving aorta and its major branches. These medium to large arteries contain elastic lamina, which is the initial site of inflammation in GCA. It is worth noting that extracranial vessel involvement can be subclinical and asymptomatic, and can be detected in imaging. Involvement of intracranial (intradural) vessels are exceedingly rare, and this postulated due to the loss of elastic lamina of the cranial vessels within a few millimeters of entering the dura.

However, it is remotely possible for the dura supplied by the middle meningeal artery, (a branch of the external carotid artery) to be involved in some patients leading to dural thickening.

Joelson et al.4 reported a 69 year old man with biopsy proven GCA, with dural thickening and multifocal dural enhancement seen in magnetic resonance imaging. Dural biopsy showed foci of perivascular inflammation, with dural vessels having inflammatory infiltrates similar to the ones seen in temporary artery biopsy. Three months following treatment with high dose prednisolone, there was resolution of dural abnormalities on gadolinium enhanced MRI. The exact pathophysiology for dural vessel involvement is uncertain, but may include vasculitis affecting the first few millimetre of the vessel with elastic lamina penetrating the dura, or ischaemia/thrombosis of dural vessels or possible direct involvement of the dural vessels.4

Other causes for dural enhancements include neoplasms, chronic hypertrophic pachymeningitis, intracranial surgery, infections (fungal, tuberculosis) and sarcoidosis.5 6

Complications of stroke (3%), seizure or cerebral dysfunction may arise as a sequelae of internal carotid
and vertebral arteries involvement in GCA.

Analysis of 463 patients with intracranial vasculitis in Mayo clinic, only two patients had intracranial vasculitis attributable to GCA. First case, 67 year old lady with established GCA more than 1 year on 5mg daily prednisolone presented with progressive deterioration of memory and homonymous hemianopia and made recovery after 4 months of increased prednisolone dose.7

Second case, a 72 year old lady presented with progressive deterioration of mental status, confusion and dysarthria. Cerebrospinal fluid (CSF) protein was elevated at 73 mg/dl. She was given prednisolone 60mg daily with cyclophosphamide 100mg/day. Despite initial clinical improvement, she deteriorated 10 days later and became comatose. Computed tomography showed areas of decreased attenuation suggestive of ischaemia. She was then given intravenous methylprednisolone 500mg daily for 3 days together with increased cyclophosphamide dose of 150mg/day, however rapidly deteriorated and succumbed. Post-mortem examination showed active intracranial vasculitis over vertebral artery and multiple extensive ischaemic infarcts over parenchyma.7

Mohammed et al8 reported a 68 year old lady with GCA presenting with fluctuating altered mental status and elevated CSF protein of 54 mg/dL (14-45 mg/dL). She improved with prednisolone 60mg daily after 1 month with near normal mental status after 3 months.

Our patient had clinical evidence of intracranial vasculitis as supported by the presence of dural thickening and enhancement, as well as elevated CSF protein with negative infective screening. Despite being on high dose corticosteroids (initial intravenous hydrocortisone and subsequent prednisolone 60mg daily) he developed new episode of altered sensorium and rapidly deteriorated.

General principle of management of GCA involves induction of remission with glucocorticoids. In patients without visual symptoms, a starting daily dose of 40-60mg of prednisolone is recommended, which is then tapered to 15 to 20mg at 2 to 3 months of remission, aiming a typical dose of 5mg or lesser after 1 year of remission. However, if those with evolving visual symptoms, intravenous pulse of methylprednisolone 250-1000mg daily for 3 days is recommended. There is no consensus on the duration of maintenance therapy, however in most literature, the average duration of treatment is about 2 years. GCA has a relapse rate ranging from 34 – 75%. In patients who relapse on tapering doses of prednisolone or in those with refractory disease, tocilizumab, an interleukin 6 inhibitor is recommended at doses of 162mcg weekly subcutaneous injections. Alternatively, methotrexate can be used with minimum dose of at least 15mg weekly. In special circumstances, where patients have risk of developing glucocorticoids related adverse effects like diabetes, cardiovascular disease, osteoporosis or glaucoma, adjunctive immunosuppressive therapy either with tocilizumab or methotrexate may be initiated together with prednisolone from the outset, to facilitate more rapid glucocorticoid tapering regimens.9

Data for other immunosuppressive agents are limited or derived from low-quality studies including for azathioprine, leflunomide, cyclophosphamide, dapsone, abatacept and ustekinumab. On the contrary, cyclosporine, adalimumab and infliximab showed no benefit in treatment of GCA.9

Our patient had underlying diabetes mellitus, hypertension and end stage renal disease with significant risk for cardiovascular events. Hence, he was started with a combination therapy of prednisolone and azathioprine to minimize glucocorticoid exposure. Methotrexate was not used due to contraindication in end stage renal disease.

Although in principle, treatment with glucocorticoids helps to prevent further visual loss, however in reality, some patients may continue to have progressive visual loss in the affected eye and may even have involvement the second normal eye while on treatment. Hoffman et al10 demonstrated 18% prevalence of visual loss among 98 patients with GCA at baseline and 14% incidence of new visual loss at 1 year despite patients being placed on 3 months high dose glucocorticoids followed by a tapering regime. Significant vision loss persisting for hours carries the risk of permanent blindness despite prompt use of high dose intravenous glucocorticoids. A prior history of amaurosis fugax is a strong predictive factor for future risk of sudden and permanent blindness.
**Conclusion:**

GCA is a quintessential differential diagnosis in all patients above 50 years presenting with new onset of headache. Visual impairment is a feared complication as it can result in permanent blindness, even with prompt treatment with glucocorticoids. Normal optic disc findings in patients with visual impairment can be due to posterior ischaemic optic neuropathy or cortical infarct, and requires high index of clinical suspicion. GCA can also present with complex ophthalmoplegia and orbital apex syndrome. As highlighted in this case, altered sensorium in GCA, in the absence of stroke, may suggest intracranial vasculitis and dural involvement, albeit rare and can lead to mortality.

**Conflict of interest**

All authors declare that they have no conflict of interest

**Funding**

There was no funding received for this paper.

**References**

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