

Severe Intracranial Involvement in Giant Cell Arteritis: 5 Cases and Literature Review

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ABSTRACT. Objective. Involvement of intracranial arteries in giant cell arteritis (GCA) is rare. We describe the neurologic complications of intracranial GCA (IC GCA) and available treatment options.

Methods. We describe 5 IC GCA cases from 3 Canadian vasculitis centers and review the literature. We searched English-language publications reporting similar patients meeting American College of Rheumatology (ACR) criteria for GCA and having intracranial artery involvement diagnosed by autopsy, magnetic resonance angiography, computed tomography angiography, or conventional angiography.

Results. All 5 cases of IC GCA met ACR criteria for GCA; 4 cases had a temporal artery biopsy that was consistent with GCA. All cases experienced cerebrovascular accident(s). Arteritis involved the following vessels: intracranial internal carotid (n = 1), vertebralbasilar arteries (n = 1), or both (n = 3). All cases received aspirin and oral prednisone (preceded by intravenous methylprednisone in 3 cases), combined with an immunosuppressant in 4 cases. All patients survived; 2 had complete neurological recovery, 3 had residual neurologic sequelae. The literature review included 42 cases from 28 publications. The clinical features of the reported cases were similar to those of our 5 cases. However, mortality was 100% in untreated cases (n = 2), 58% in those treated with corticosteroid alone (n = 31), and 40% in those treated with corticosteroid and an immunosuppressant (n = 10).

Conclusion. IC GCA appears to be associated with neurologic complications and mortality. In some cases corticosteroid alone was not sufficient to prevent neurologic complications. The role of additional immunosuppressive agents needs further investigation. (J Rheumatol First Release January 15 2016; doi:10.3899/jrheum.150143)

Key Indexing Terms:

GIANT CELL ARTERITIS

STROKE

CRANIAL ARTERY

Giant cell arteritis (GCA) is large-vessel vasculitis affecting individuals over age 50 years, with a prevalence of about 3 in 10,000¹. Complications of GCA can be serious, including blindness, stroke, and aortic dissection. Cerebrovascular accidents (CVA) occur in 4% to 6% of patients with GCA². Despite being uncommon, CVA is reported as the leading cause of mortality in GCA^{3,4}. The causes of CVA in GCA are

multifactorial and include hypercoagulability and accelerated atherosclerosis from a chronic proinflammatory state, treatment complications from longterm high-dose corticosteroids, and direct damage to blood vessels from arteritis. GCA is usually limited to extracranial vessels including the carotid artery, which can contribute to risk of stroke. It has been suggested that the inflammation in GCA usually involves the elastic tissue in the artery wall, and because the intradural portions of the artery have little or no elastic tissue, they tend to be spared⁴. However, cases of intracranial portions of the internal carotid and vertebral artery have been reported^{4,5,6,7,8}. Although involvement of intracranial arteries is rare in GCA, it can lead to severe neurologic complications, such as multiple territory CVA, multiinfarct dementia, and death.

We describe 5 new cases of intracranial GCA (IC GCA) and review 42 cases in the literature to detail presentation, diagnosis, treatment, and outcomes of this rare association.

MATERIALS AND METHODS

Case series. We reviewed medical charts of 5 patients with IC GCA in 3 Canadian vasculitis specialty centers (CanVasc). All cases were diagnosed with GCA by the treating physician and they met the American College of Rheumatology (ACR) classification criteria for GCA⁹. Temporal artery

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biopsy was performed in all cases within 1 to 2 weeks of presentation, except Case 4 (biopsy was performed a month later). They presented with CVA and had evidence of intracranial vasculitis on magnetic resonance angiography (MRA), computed tomographic angiography (CTA), or conventional angiography. Data regarding age, sex, GCA and neurologic symptoms, timing of neurologic symptoms, laboratory tests [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), investigation for thrombophilia and vasculitis], imaging studies, treatments, and outcomes were collected from medical records. Research Ethics Board Approval from participating institutions was obtained.

Systematic literature review. We searched the following databases: PubMed, Embase (1950–December 2012), and the Cochrane library (up to December 2012). Abstracts from ACR (2009–2012) and European League Against Rheumatism (EULAR) annual meetings were searched (2009–2012). Our literature search combined the terms “giant cell arteritis,” “temporal arteritis,” “stroke,” and “multi-infarct dementia” (for full search strategy see Appendix 1). A hand search of references in relevant articles was also conducted to identify additional cases.

Publication selection. Two authors (RA and LB) independently conducted the literature search and screened citations. Citations were first screened by title and abstract to retrieve relevant articles. The retrieved articles were then reviewed in full, applying the following inclusion criteria: GCA diagnosed by treating physician based on clinical presentation, temporal artery biopsy, inflammatory markers, and/or imaging; ACR classification criteria for GCA with at least 3 out of 5 criteria met or a temporal artery biopsy consistent with GCA; CVA diagnosed by treating physician based on clinical symptoms and imaging; and involvement of the intracranial portions (within the skull) of the internal carotid artery (ICA) and its branches, vertebral artery, or basilar artery. Intracranial involvement for ICA and vertebral artery was classified into: (1) extradural: intracranial segment of vessel prior to dural perforation; and (2) intradural: intracranial segment after piercing the dura⁴. This distinction was included based on reports that suggested that intradural involvement was exceedingly rare⁴ and may be associated with worse outcomes. Patients with only extracranial involvement were excluded. Vessel involvement had to be determined by autopsy (histologic examination), MRA, CTA, or conventional angiography. Diagnosis made by duplex ultrasonography was excluded. Articles in a language other than English were excluded.

Data extraction. From the selected articles we extracted the publication details, followup times, clinical presentation, ESR, biopsy and imaging investigations, treatment, outcomes, and, if applicable, autopsy reports. We did not collect CRP values because these were not reported in the majority

of papers. Definitions of complete versus partial recovery were heterogeneous across studies. We defined “no residual neurologic symptoms” based on physician opinion as complete recovery and “any residual neurologic symptoms” as partial recovery.

RESULTS

Case series. The characteristics of our 5 cases with IC GCA are summarized in Table 1. All cases had at least 1 risk factor for atherosclerosis. All had a temporal artery biopsy that was consistent with GCA, except Case 5, who had a normal temporal artery on biopsy. Hypercoagulable state and systemic vasculitis were ruled out in all cases. All were treated with corticosteroids and aspirin (ASA; 3 at diagnosis and 2 after CVA) and 4/5 with additional immunosuppressant(s). In applicable cases, the management of cardiovascular risk factors was optimized. Classic GCA symptoms improved within 48 h of starting treatment. All patients survived with no relapses requiring increased corticosteroids or the additional immunosuppressive agents during their followup. Two of the 5 had complete neurologic recovery and the remaining had mild impairments; improvement in neurologic symptoms occurred slowly over the course of followup.

Case 1. A 75-year-old man presented with headaches and painless vision loss. He had evidence of arteritic ischemic optic neuropathy in the left eye. Prednisone 80 mg was initiated. Two weeks later, he presented with disorientation, receptive aphasia, behavior changes, acute apraxia, and right-side weakness. MRA of the head showed severe narrowing of the left ICA and irregularities in both posterior cerebral arteries (Figure 1A). He was given ASA and high-dose prednisone 80 mg was continued. A month later, he presented with worsening confusion and personality changes. MRA of the head showed 2 new infarcts within the left middle cerebral artery (MCA) territory in the left frontal lobe. CTA of the head showed progressive narrowing of the left ICA lesion to the point of near occlusion distally. He

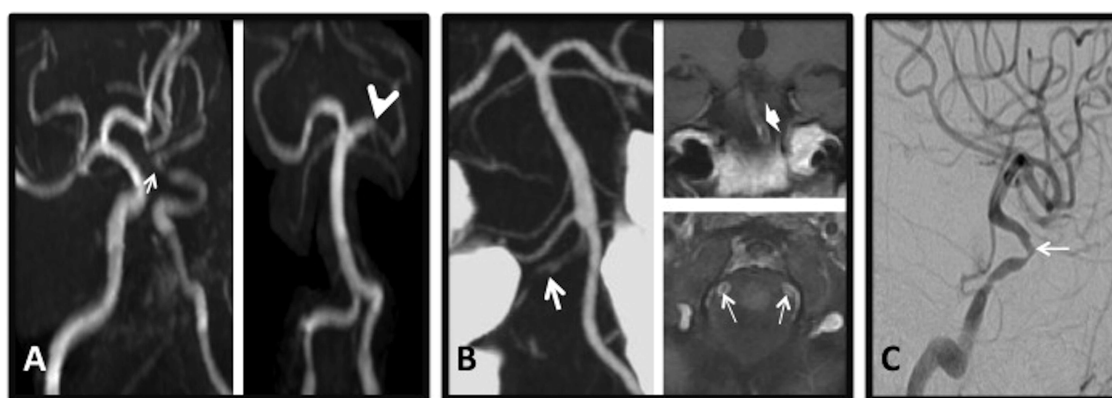


Figure 1. Imaging of intracranial vessels. A: Case 1. Maximum intensity projections of flow-sensitive magnetic resonance angiography show severe stenosis at the supraclinoid left internal carotid artery (thin white arrow) and irregularity of the left posterior cerebral artery (white arrowhead). B: Case 2. Computed tomography angiogram shows near occlusion of the right intradural vertebral artery (left). Post-contrast MRI shows abnormal mural enhancement of the basilar artery (top right) and vertebral arteries bilaterally (bottom right). C: Case 3. Digital subtraction angiogram shows severe narrowing at the anterior genu of the left internal carotid artery.

Table 1. Characteristics of 5 patients with intracranial giant cell arteritis (IC GCA).

Case, Age /sex	Vascular Risk Factors	Clinical Signs and Symptoms at Presentation	ESR*, CRP mm/h	Brain MRI or CT	Brain MRA	Temporal Artery Biopsy	Treatment	Followup	Outcome
1, 75/M	Hypertension, dyslipidemia	Headache, unilateral visual loss (optic neuropathy); 2 weeks later: transient right hemiparesis, confusion, aphasia, apraxia; 4 weeks later: worsening confusion, personality changes	74	MRI: PCA territory infarction, 2 new left frontal lobe infarcts	CTA/MRA: supraclinoid left ICA severe stenosis and bilateral PCA irregularity and narrowing peripherally	Typical GCA**	Oral prednisone, IV cyclophosphamide, methotrexate, aspirin	3 yrs	Mild cognitive impairment
2, 82/M	Diabetes, hypertension, dyslipidemia	Right scalp tenderness, jaw claudication, vertigo, blurry vision and diplopia, dysarthria, right pronator drift, facial droop	37	MRI: bilateral cerebellar, pontine infarction	CTA: right intradural VA near occlusion. Left intradural VA and BA irregular with abnormal mural enhancement of the basilar and VA bilaterally on postcontrast MRI	Positive not typical***	IV methylprednisone, oral prednisone, IV cyclophosphamide, methotrexate, aspirin, tissue plasminogen activator	10 mos	Mild dysphagia
3, 66/F	Diabetes, hypertension, dyslipidemia	Headache, blurry vision. 1 week later: confusion, mild dysarthria, aphasia, right facial droop, unilateral hemiparesis and hemi-sensory loss	20	CT: Left frontal lobe infarction	CTA/MRA/angiogram: left ICA had high-grade stenosis in the cavernous/anterior genu segments, mild stenosis in the right ICA. Irregular VA and BA	Typical GCA**	IV methylprednisone, oral prednisone, IV cyclophosphamide, aspirin, clopidogrel; left ICA angioplasty	5 yrs	Unilateral facial droop and mild decrease in power
4, 40/M	Hypertension, dyslipidemia, smoking	Occipital and temporal, frontal headaches. 1 month later: left-sided facial droop, left facial numbness, decreased blinking and dysarthria. 1 month later: upper limb sensory disturbance	35	MRI: several punctuated areas of restricted diffusion within the deep white matter of the right MCA and right PICA	Conventional angiogram: multifocal narrowing and irregularities in ACA, right distal MCA branches, bilateral posterior circulation	Typical GCA**	Oral prednisone, aspirin	2 yrs	Complete recovery
5, 70/F	Dyslipidemia	Headache, scalp tenderness, jaw claudication, blurry vision. 3 weeks later: word-finding difficulty, dysarthria, hemiparesis	108	Left frontal lobe infarct	MRA: Bilateral ICA critical stenosis/ near occlusion (supraclinoid region)	Negative	IV methylprednisolone, oral prednisone, methotrexate, clopidogrel, aspirin	3 yrs	Complete recovery

*ESR and CRP measured at the time of GCA diagnosis. **Typical temporal artery biopsy: sample size at least 2 cm, necrotizing arteritis with a predominance of mononuclear cells or a granulomatous process with multinucleated giant cells. ***Biopsy showed intimal thickening, mural calcification, focal disruption of the internal elastic lamina, and mild lymphoplasmacytic infiltrate in small adventitial blood vessels. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MRI: magnetic resonance imaging; CT: computed tomography; MRA: magnetic resonance angiography; ICA: internal carotid artery; PCA: posterior cerebral artery; IV: intravenous; CTA: computed tomographic angiography; BA: basilar artery; VA: vertebral artery; ACA: anterior cerebral artery; MCA: middle cerebral artery; PICA: posterior inferior cerebral artery.

started intravenous (IV) cyclophosphamide (CYC) 1 g monthly for 6 doses followed by subcutaneous (SC) methotrexate (MTX) 25 mg/week. His prednisone was continued at 80 mg daily, then gradually tapered to 5 mg daily over a 5-month period. Over the 3-year followup, his cognition and weakness improved. He has not developed any new deficits or strokes. MRA performed 1 year after diagnosis did not show any disease progression.

Case 2. An 82-year-old man with polymyalgia rheumatica presented with a 2-week history of right scalp tenderness, jaw claudication, vertigo, blurry vision, and diplopia. Subsequently he had dysarthria, right-side arm weakness, and a facial droop. He was treated acutely with IV tissue plasminogen activator. He had scattered cerebellar infarcts and left pontine infarct on cerebral MRI. CTA showed caliber irregularities along the cervical vertebral arteries bilaterally. The intradural right vertebral artery was almost occluded, while the left intradural vertebral artery and basilar artery were irregular in caliber. There was abnormal mural enhancement of both the intradural vertebral artery and the basilar artery (Figure 1B). He was treated with IV methylprednisolone 1 g/day for 3 days followed by prednisone 70 mg/day. He was given IV CYC 1 g monthly for 7 doses, followed by MTX 25 mg/week SC for maintenance. His prednisone was tapered to 5 mg daily. ASA was continued. He recovered completely except for some mild dysphagia and is doing well 10 months after his initial presentation. MRA performed 1 year after diagnosis did not show any disease progression.

Case 3. A 66-year-old woman with GCA who was treated with prednisone 80 mg/day developed symptoms of confusion, aphasia, mild dysarthria, right facial droop, right-side weakness, and sensory impairment during 1 week when the prednisone was diminished to 40 mg/day. CT of the head showed new infarcts in the left frontal lobe. Cerebral CTA and MRA showed a high-grade stenosis in the left ICA in the cavernous/anterior genu segments, mild stenosis in the right ICA, and vessel irregularity in the distal branches of the external carotid artery. The intracranial and extracranial vertebral arteries were small and irregular as was the basilar artery. Findings were further confirmed with conventional angiography (Figure 1). The patient was treated with ASA and IV methylprednisolone 1 g daily for 3 days, followed by oral prednisone 70 mg/day and IV CYC 1 g monthly for 6 doses. She also had a left cavernous ICA angioplasty because of progressive worsening of the stenosis over time. Clopidogrel 75 mg daily was added. Five years later, she has mild right facial droop and mild decrease in power on the right side and has not had any recurrent strokes. MRA performed 1 year after diagnosis did not show any disease progression.

Case 4. A 40-year-old man presented with bilateral occipital headaches¹⁰. A month later he presented with left-side facial droop, left facial numbness, decreased blinking, and dysarthria. He was diagnosed with Bell's palsy and was

treated with prednisone 40 mg/day for 5 days and ASA. His facial palsy resolved but headache continued. A month later he developed left upper limb sensory disturbance. Lumbar puncture revealed inflammatory cerebrospinal fluid. A brain MRI showed several punctate areas of restricted diffusion within the deep white matter of the right MCA and right posterior inferior cerebellar artery territories. Conventional cerebral angiogram showed diffuse areas of multifocal narrowing and irregularities within the right anterior cerebral artery (ACA) and distal MCA branches; milder irregularities were found in the left ACA and bilateral posterior circulation vessels. A temporal artery biopsy was performed and was consistent with GCA. Prednisone 80 mg daily was initiated with complete resolution of symptoms. He continued to do well with gradual prednisone taper and did not develop recurrent neurologic symptoms over 2 years of followup.

Case 5. A 70-year-old woman with new-onset GCA, treated with prednisone 50 mg daily and ASA, developed word-finding difficulty, dysarthria, and right hemiparesis 3 weeks later. MRI of the head revealed an acute ischemic infarct in the left frontal lobe, and bilateral critical stenosis or near-occlusion of the terminal portion of both ICA in the supraclinoid region, with some milder stenosis within the petrous segments of both ICA. This stenosis was in relative isolation with no other changes of significant atherosclerosis within the ICA bulbs, proximal vessels, or aortic arch. She was treated with clopidogrel 75 mg daily, IV methylprednisolone 1 g daily for 5 days, followed by prednisone 50 mg and MTX 25 mg orally weekly. Three years later she is still in complete remission, taking MTX and prednisone.

Literature review. Search results are shown in Figure 2; 28 articles and 42 cases met our inclusion criteria^{3,4,7,8,11-34}. In our analysis we also included our 5 cases for a total of 47 cases with IC GCA. Our cases had characteristics similar to those found in the literature. We had 1 patient who was under 50 years of age; however, this patient had a temporal artery biopsy consistent with GCA¹⁰.

Demographics and clinical features of IC GCA cases. Forty-five cases (96%) were over age 50 years and the mean age at the time of neurologic symptoms was 71 years. There were 19 women (42%). Data on cardiovascular risk factors (diabetes, hypertension, hyperlipidemia, obesity, and smoking) were available for 22 cases (47%). Of those, 10 (45%) had 1 risk factor, 8 (36%) had 2 or more risk factors, and 4 (18%) had no risk factors.

The majority of cases (30/47; 64%) developed CVA after GCA symptoms or diagnosis. The median time until CVA was 60 days (range 7 to 6205). Eight (17%) developed CVA at the same time they presented with GCA symptoms. Nine (19%) had no GCA symptoms at any point during the disease course, but met ACR criteria by having a positive temporal artery biopsy (7 cases) or a positive histopathology of temporal artery postmortem (1 case).

Table 2 summarizes the clinical features of the 47 cases.

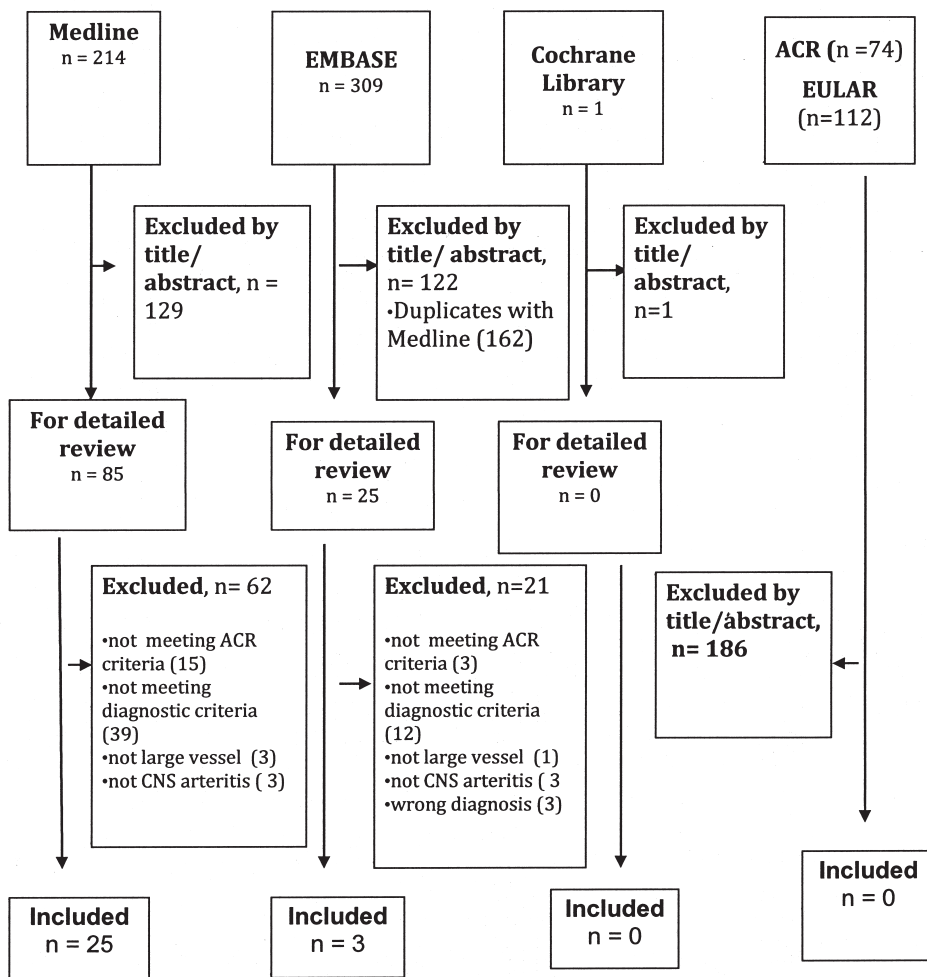


Figure 2. Literature search results. “Not meeting diagnostic criteria”: cranial vasculitis not proven on magnetic resonance angiography, computed tomography angiography, or autopsy. ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; CNS: central nervous system.

As expected, the most common GCA symptom was headache, in 34 cases (72%). A high proportion (26%) experienced unilateral blindness. Only 30 cases (64%) had an elevated ESR at the time of diagnosis. The most common neurologic manifestations were cerebellar (34 cases; 72%), motor impairment (29 cases; 62%), and altered level of consciousness (23 cases; 49%).

Treatment and outcomes of patients with IC GCA. Drug therapies used in the IC GCA cases are summarized in Table 3. Twenty-nine cases were not receiving corticosteroid at the time of stroke. Of these, 8 had stroke as the presenting feature of GCA, 8 had no classic GCA symptoms, 12 had a missed diagnosis of GCA, and 1 could not tolerate prednisone. Three cases had been tapered to doses of prednisone below 10 mg daily at the time of stroke. Ten cases received an immunosuppressive agent in addition to high-dose corticosteroids; of these, 1 had angioplasty. Another case had angioplasty in addition to corticosteroids. Three out of 45 cases were

receiving ASA prior to stroke. After the diagnosis of stroke, 10 were started on ASA, 6 on clopidogrel, and 12 on anticoagulation. Twenty-seven cases (57%) were not reported to be receiving any antiplatelet or anticoagulant agents.

The overall mortality was high (24/45; 53%). Of the survivors, 10 cases (22%) had complete neurologic recovery. The cause of death was attributable to complications of IC GCA in most cases; 4 cases (9%) died from infectious complications. Mortality was 60% (10/17) when vertebrobasilar arteries were involved and 81% (9/11) for extradural disease compared to 48% (16/33) for intradural disease. Mortality in the cases not treated with corticosteroids or who were receiving prednisone doses below 10 mg daily at the time of stroke was similar to those receiving higher doses of corticosteroids (56% vs 50%, respectively). Two cases were not receiving any treatment throughout the course of their disease and both died from cerebrovascular complications. Cases treated with an immunosuppressive agent in

Table 2. Clinical features of IC GCA and distribution of affected vessels (n = 47).

Clinical features	n (%)
GCA symptoms	
Headache	34 (72)
Systemic symptoms*	24 (51)
Temporal artery abnormalities/scalp tenderness	19 (40)
Nonsevere visual symptoms**	18 (38)
Unilateral blindness	12 (26)
Jaw claudication	11 (23)
PMR	10 (21)
Neurologic symptoms	
Cerebellar†	34 (72)
Motor	29 (62)
Altered LOC/coma	23 (49)
Cranial nerves	19 (40)
Cognitive/memory decline	12 (26)
Speech	10 (21)
Sensory	10 (21)
Timing of neurologic symptom in relation to GCA symptoms	
Same time as GCA symptoms	8 (17)
No GCA symptoms	9 (19)
After GCA symptoms	30 (64)
Disease distribution‡	
Territory involved	
Vertebrobasilar territory	17 (36)
Carotid territory	6 (13)
Both territories	24 (51)
Location with respect to dura	
Intradural	33 (70)
Extradural	12 (26)
Unknown	2 (4)

*Systemic symptoms include anorexia/weight loss, fever, fatigue, and myalgia. **Visual symptoms include blurry vision and eye pain. † Gait ataxia: 20 (59), dysarthria: 17 (50), diplopia: 10 (29), vertigo: 9 (26), nystagmus: 7 (21), incoordination: 6 (18). ‡ Determined using the following: MR angiogram: 18 (38), autopsy: 14 (30), conventional angiography: 13 (28), or CT angiogram: 2 (4). IC GCA: intracranial giant cell arteritis; PMR: polymyalgia rheumatica; LOC: level of consciousness.

addition to corticosteroids had lower mortality, 4 out of 10 (40%) versus 18 out of 31 (58%) in the cases treated with corticosteroids only. Four of 8 cases treated with CYC died: 1 from pneumonia, 1 from line sepsis post-angioplasty, and 2 died shortly after presentation from severe stroke complications.

DISCUSSION

We describe a total of 47 GCA cases (5 new) with IC involvement. Cerebral vascular events occurred after the diagnosis of GCA in 64%, with a median duration of 60 days. A large proportion of cases were not receiving prednisone (64%) or aspirin (93%) at the time of CVA. Significant morbidity and mortality was associated with IC GCA: mortality was 53% with a median time to death of 12 days; of the cases who survived, 24% had residual neurologic deficits.

Given the significant complications associated with IC

GCA, it is important to identify these patients early. There are no published studies that investigate predictors for intracranial vasculitis in patients with GCA. We found that in IC GCA, the proportion of males (58%) and prevalence of blindness (26%) was higher, and the prevalence of polymyalgia rheumatica and jaw claudication was lower (21% and 23%, respectively) than previously reported for GCA^{2,35,36}. However, we cannot make any conclusions regarding screening, especially because the incidence of IC GCA is unknown. CVA in GCA is reported to occur in 4%–6%², but the proportion attributable to IC vasculitis versus atherosclerosis remains unclear. The presence of active GCA symptoms at the time of CVA may suggest IC vasculitis. However, we found that 19% of cases did not have any GCA symptoms before or at the time of CVA, and upon autopsy some of these cases were shown to have active IC arteritis.

We also observed that IC GCA commonly presented with multiterritory CVA, with a predilection for vertebrobasilar arteries. This can be distinguished from atherosclerotic disease, which more commonly affects the middle cerebral arteries^{4,37}.

The diagnosis of IC GCA is also limited by the available imaging modalities. Although conventional angiography is the most sensitive, it is not specific for vasculitis, particularly in patients with concomitant atherosclerotic disease. Findings that support vasculitis include alternating areas of stenosis and dilatation in the second- and third-order arterial branches and venous territories; and less commonly, long-segment stenosis and pseudoaneurysms³⁸. CTA and MRA evaluate the vessel wall and lumen³⁹. However, specific signs of vasculitis (vessel wall edema, mural contrast enhancement, and circumferential vessel wall thickness) may not be detected in smaller vessels, especially when not using 3-T MRI¹⁸. Positron emission tomography has been shown to be more sensitive than MRI⁴⁰, but it is not widely available, provides limited anatomical visualization, and may be falsely positive in acute atherosclerotic vascular disease⁴¹.

If IC GCA is suspected, there are no controlled or observational studies to guide treatment decisions. We found lower mortality in patients who started receiving immunosuppressive agents in conjunction with corticosteroids compared to those who received corticosteroids alone (40% vs 58%, respectively). Prednisone and methylprednisone inefficiently cross the blood-brain barrier, which may make treating central nervous system vasculitis with these agents difficult; this raises the question whether dexamethasone should be used⁴². However, only one of the reported cases used dexamethasone, so there is insufficient information to comment on its effectiveness in treating IC GCA compared to other corticosteroids. Several studies examined using immunosuppressive agents in conjunction with corticosteroids in GCA^{43,44,45}. In a metaanalysis, MTX was shown to be better than placebo in preventing relapse of GCA. It is also an

Table 3. Treatments and outcomes of IC GCA cases (n = 45).

	N (%)	Followup, Median No. Mos (range)	Recovery		Death, n (%)	Time to Death, Median No. Days (range)
			CR, n (%)	PR, n (%)		
Corticosteroids alone	31 (69)	3 (1–85)	6 (19)	7 (23)	18 (58)	10 (1–120)
Corticosteroids and methotrexate or azathioprine	2 (4)	35 (NR)	2 (100)	0	0	NA
Steroids and CYC	3 (7)	NA	NA	NA	3 (100)	160 (12–540)
Corticosteroids, methotrexate, and CYC	2 (4)	23 (10–36)	2	2 (100)	0	NA
Corticosteroids, angioplasty, and CYC	3 (7)	13 (1–24)	0	2 (67)	1 (33)	210
Corticosteroids and angioplasty	1 (2)	48	1 (100)	0	0	NA
Corticosteroids and surgery*	1 (2)	NR	1 (100)	0	0	NA
No treatment	2 (4)	NA	NA	NA	2 (100)	3.5 (2–5)
Total	45	5 (1–85)	10 (22)	11 (24)	24 (53)	12 (1–540)

*Superficial temporary artery to MCA bypass. Initial corticosteroids: oral prednisone (n = 27; mean dose 60 mg for 2–3 weeks), IV methylprednisone 1 g daily for ≤ 3 days (n = 7), IV methylprednisone 1 g daily for ≥ 5 days (3), IV methylprednisone 1 g daily for unknown duration (n = 3), other corticosteroids (n = 3). Note: treatment and outcome was not reported in 2 patients. CR: complete recovery from neurologic deficits; PR: partial recovery; IC GCA: intracranial giant cell arteritis; NA: not applicable; NR: not reported; MCA: middle cerebral artery; IV: intravenous; CYC: cyclophosphamide.

effective steroid-sparing agent⁴⁵. CYC has also shown potential benefit as a corticosteroid-sparing agent in patients with GCA⁴³, and there is evidence supporting its use in primary angiitis of the central nervous system⁴⁶.

Given that a large proportion of IC GCA cases had at least 1 risk factor for atherosclerotic disease (> 80%), and that GCA bears an increased risk of cardiovascular events⁴⁷ and possible worsening of preexisting cardiovascular comorbidities by corticosteroids, the management of modifiable cardiovascular risk factors in GCA is critical. Unfortunately, the majority of the articles included in this review did not report how cardiovascular risk factors were managed. Based on 2 recently published metaanalyses, antiplatelet therapy appears to be beneficial in subjects with GCA^{48,49}. Only 57% of the reported IC GCA cases were started on an antiplatelet or anticoagulant therapy although they all experienced a CVA.

Our study has several strengths: we carefully characterized vascular risk factors, imaging findings, treatment, and outcomes. Our newly reported cases were managed in an interdisciplinary clinic (rheumatology, neurology, ophthalmology, pathology, and neuroradiology); several imaging modalities were used to confirm diagnosis of IC GCA and atherosclerotic CVA was ruled out. The cases had very good neurological outcomes. The presentation and clinical outcomes of our cases were similar to those in a recent series that described 4 cases of IC GCA that were also treated aggressively with combinations of corticosteroids and immunosuppressants⁵⁰. From the literature review, the mortality of IC GCA may be an overestimate, because severe cases tend to be more commonly reported. Alternatively, underreporting might also be a problem: CVA secondary to GCA might be misdiagnosed because of the lack of classic GCA symptoms, or CVA in patients with GCA may be wrongly attributed to atherosclerotic disease.

IC GCA is a serious condition and may be associated with

neurologic complications and mortality. When GCA is diagnosed, physicians should maintain a high index of suspicion for intracranial involvement, particularly in patients with neurologic symptoms and vision loss. If IC GCA is suspected, imaging should be performed to confirm intracranial vasculitis and to distinguish it from atherosclerotic disease. Controlled drug studies for IC GCA are lacking. However, it can be treated like complicated GCA following current published guidelines with IV methylprednisolone followed by 1 mg/kg prednisone. Alternatively, dexamethasone may be a better corticosteroid option for IC GCA, as it crosses the blood-brain barrier more efficiently⁴². Concomitant cardiovascular risk factors are common in IC GCA and must be managed. Antiplatelet therapy should be considered for all patients with GCA and should be initiated in patients with arterial thromboembolic events without contraindications. We found that in some cases corticosteroid alone was not sufficient to prevent neurologic complications; it may be necessary to add other immunosuppressive agents, such as MTX or CYC depending on the severity of the disease. Larger studies are needed to better characterize IC GCA, determine optimal treatment, and improve outcomes.

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APPENDIX 1. Complete search strategy.

EMBASE

1. Keywords: Giant cell arteritis or GCA or temporal arteritis or Giant cell angiitis. Emtree: Giant cell arteritis
2. Keywords: cerebrovascular accident or CVA or stroke or brain/ cerebral/ cerebellar/ cerebral artery infarct or transient ischemic attack or TIA or intracranial/cerebral AND thromb or dementia or internal carotid/ vertebral/ basilar/ vertebrobasilar AND occlusion/ stenosis/ insufficiency or posterior circulation or neurology
EMTREE: cerebrovascular disease or brain ischemia or transient ischemic attack or brain infarction/ brainstem infarction/ cerebellum infarction or occlusive cerebrovascular disease or basilar artery obstruction or middle cerebral artery occlusion or vertebral artery stenosis or cerebral artery disease or vertebrobasilar insufficiency or cerebrovascular accident or lacunar stroke or anterior cerebral artery/ middle cerebral artery/ posterior cerebral artery/ basilar artery/ anterior communicating artery/ posterior communicating artery/ posterior inferior cerebellar artery/ brain circulus arteriosus/ meningeal artery

Medline:

1. Keywords: Giant cell arteritis or GCA or temporal arteritis or Giant cell angiitis. MeSH: Giant cell arteritis
2. Keywords: cerebrovascular accident or CVA or stroke or brain/ cerebral/ cerebellar/ cerebral artery infarct or transient ischemic attack or TIA or intracranial/cerebral AND thromb or dementia or internal carotid/ vertebral/ basilar/ vertebrobasilar AND occlusion/ stenosis/ insufficiency or posterior circulation or neurology
MeSH: cerebrovascular disorders or brain ischemia or brain infarction or ischemic attack, transient or vertebrobasilar insufficiency or cerebral small vessel disease, stroke, lacunar or dementia, vascular or dementia, multi-infarct or intracranial arterial disease or cerebral arterial disease or infarction (anterior, middle, posterior) cerebral artery or intracranial thrombosis or stroke or vasculitis, central nervous system

Cochrane:

1. Keywords: Giant cell arteritis or GCA or temporal arteritis or Giant cell angiitis. MeSH: Giant cell arteritis
 2. Keywords: cerebrovascular accident or CVA or stroke or brain/ cerebral/ cerebellar/ cerebral artery infarct or transient ischemic attack or TIA or intracranial/cerebral AND thromb or dementia or internal carotid/ vertebral/ basilar/ vertebrobasilar AND occlusion/ stenosis/ insufficiency or posterior circulation or neurology
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