Giant cell arteritis

Giant cell arteritis is the most common chronic granulomatous vasculitis, mainly involving large and medium-sized vessels, and it almost exclusively affects patients older than 50 years. The initial event that triggers the cascade of immune-mediated responses and subsequent inflammation is unknown. No specific test can confirm the diagnosis, but temporal artery biopsy is considered the gold-standard. Awareness of common clinical presentations is important, but occult or uncommon features may be mistaken for other pathology. Glucocorticoids remain the cornerstone of therapy—they can prevent but not reverse vision loss.

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Giant cell arteritis, also referred to as cranial or temporal arteritis, is an immune-mediated chronic granulomatous vasculitis mainly involving large and medium-sized vessels. Although it may be widespread, symptomatic vessel inflammation usually involves cranial branches of arteries originating from the aortic arch.[1] Almost any artery as well as some veins may be affected.

The first clinical description of giant cell arteritis was reported in 1890.[2] However, its first histological appearances were reported in 1932 by Horton and colleagues, who also coined the term temporal arteritis.[3] The term giant-cell arteritis, secondary to the presence of multinucleated giant cells, was offered in 1941.[4] It is the most common vasculitis in older patients. Although deemed a multisystem disease, visual symptoms are often the presenting feature. Imminent danger of bilateral total blindness, which may be preventable, means that early identification and institution of appropriate treatment is important. Its variable clinical presentations, lack of perfect diagnostic test, and devastating complications often present a diagnostic challenge.

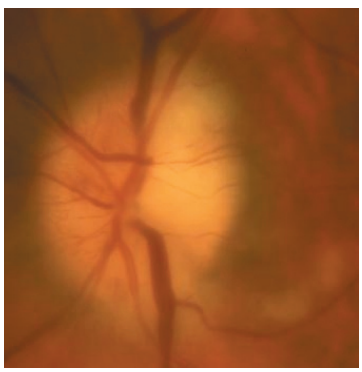

Figure 1: Optic disc oedema

Giant cell arteritis predominantly affects white patients older than 50 years, typically in the seventh and eighth decades of life, with women affected twice as often as men.[5] The incidence increases from 23 per 100,000 people per year in the sixth decade of life to 44·7 per 100,000 people per year in the ninth decade of life and older.[6,7] It is most prevalent among Scandinavians and Northern Europeans, with 17–18 cases per 100,000 in at-risk populations.[7]

Despite significant advances in understanding of the pathogenesis of giant cell arteritis in recent years, a single causative agent remains to be identified. The initial event that triggers the cascade of immune mediated responses and subsequent inflammation is still unknown. Table 1 shows known risk factors.

Histopathogenesis

The most probable determinant of arterial susceptibility to this disorder is the presence or quantity of internal elastic lamina within the vessel wall. For example, intracranial cerebral vasculature is not affected in giant cell arteritis because these vessels lack an internal elastic lamina.[18]

The extracranial vertebral, superficial temporal, posterior ciliary, and ophthalmic arteries are most commonly involved. The internal

and external carotid and central retinal arteries are affected somewhat less frequently[19] The vasculitis is a panarteritis with transmural inflammation involving the media, intima, and adventitia of the vessel. The varied course of the disease may result in skip lesions, which are essentially segments of artery not affected by inflammation adjacent to areas of inflammation.[20] The classic histological picture is characterised by a granulomatous inflammatory infiltrate with lymphocytes, macrophages, and multinucleated giant cells. However, only about 50% of routine biopsy samples show all these typical features.

Vessel occlusion in giant cell arteritis is secondary to intimal hyperplasia induced by several inflammatory mediators, particularly platelet derived growth factor and interferon-γ. Inflammatory changes are mediated by several different cytokines Interleukins 1 and 6 (IL-1, IL-6), tumour necrosis factor (TNF)-α, and transforming growth factor β-1, all of which have been demonstrated in the segments of affected vessels.[21,22] Production of these cytokines from macrophages is responsible for the systemic manifestations of giant cell arteritis.

	Features
Age	Risk increases with age. It is 20 times more common in the ninth decade of life as compared with fifth and sixth decade. The exact mechanisms of immune activity in relation to age in these patients has not been investigated.
Gender	Clear predominance with 2–4 fold more women than men.[5] One Spanish study only has shown male predominance.[8]
Genetic	Association of giant cell arteritis and visual complications with HLA-DRB1*04 alleles.[9,10] Genetic polymorphisms in expression of TNF, intercellular adhesion molecule (ICAM-1) and interleukin receptor agonist (IL-IRA) influence susceptibility.[11]
Smoking	Smoking is a significant risk factor; however, manifestations of atherosclerosis such as hypertension and ischaemic heart disease are not significantly related to giant cell arteritis.[12,13]
Female sex hormones	The number of pregnancies was lower among patients with giant cell arteritis in comparison with controls.[14] Oestrogen levels may confer some protection. Whether reduction in circulating levels in post-menopausal women is a risk factor requires further study.
Environment factors	Seasonal variations are seen with peaks in late winter, autumn and summer.[15]
Diabetes	Diabetes appears to cut the risk of developing giant cell arteritis in half.[13]
Infectious agents	Epidemiological observations, reports, and studies using DNA detection techniques implicate Chlamydia pneumoniae, Mycoplasma pneumoniae, and parvovirus B19 as triggers.[16,17]

Table 1: Risk factors for giant cell arteritis

Clinical features

Giant cell arteritis can manifest in several ways (table 2). The onset of symptoms may be insidious or abrupt. The spectrum of clinical features is wide and can be attributed to local vascular injury, ocular involvement and systemic inflammation.Although doctors need to be aware of the common presenting features, the recognition of atypical presentations as silent or occult giant cell arteritis is more challenging but occurs in up to 38% of patients.[23]

Physical examination

The general physical examination may be unremarkable. Weight loss might be evident and patients may look chronically ill (fever, tender joints, and muscles). Usually there is no muscular weakness, unless it is secondary to mononeuropathy or polyneuropathy.

Thickened, nodular, tender, and pulseless temporal arteries are a classic sign but temporal arteries may also be normal on examination.[1] Opthalmoscopic examination in the initial stages presents as optic disc oedema (figure 1) and eventually results in ischaemia of the optic nerve head and optic atrophy with permanent partial or complete loss of vision in one or both eyes. Occasionally, there is posterior ischaemic optic neuropathy, central retinal artery occlusion, cilioretinal artery occlusion or ocular

	Feature
General	• Normochromic normocytic anaemia • Weight loss • Malaise • Pyrexia of unknown origin, usually low-grade, but may reach 39°C*
Local	• Headache of temporal and occipital areas; no pattern; severe; sometimes throbbing • Scalp tenderness—often temporal, elicited by touch • Jaw claudication—elicited by talking or chewing
Ocular	• Partial or complete vision loss; sudden and painless; seen in 20% of patients. • Unilateral or bilateral blindness • Amaurosis fugax—may precede visual loss in up to 44% of patients. • Diplopia • Visual hallucinations* • Eye pain* • Ocular muscle paresis*
Respiratory	• Cough* • Sore throat* • Hoarseness of voice; seen in 10% of patients • Pleural effusion*
Cardiovascular	• Aortic regurgitation* • Tissue gangrene of scalp, tongue or extremities.* • Intestinal infarction* • Myocardial infarction* • Pericardial effusion* • Aortic aneurysm* • Aortic dissection* • Limb claudication* • Raynaud's phenomenon* • Lingual infarction* • Tongue infarction*
Neurological	• Peripheral neuropathy* • Transient ischaemic attack or stroke in carotid or vertebro-basilar distribution* • Dementia* • Memory impairment*
Musculoskeletal	• Polymyalgia rheumatica; (around 40% of patients) • Peripheral arthritis – in about 25% of patients.
Tumour-like lesions	• Breast mass* • Uterine mass* • Ovarian mass*
Endocrine	• Syndrome of inappropriate antidiuretic hormone hypersecretion*

Table 2: Clinical manifestations[1,22,24,25,27,29,30]

*An uncommon feature of giant cell arteritis

muscle paresis.[23]

Patients with diffuse arteritis may exhibit peripheral absent pulses, difference in systolic blood pressures between arms of more than 10–15 mmHg and abnormal ankle-brachial index (<0·9) indicate significant arterial obstruction.[26,44] Bruits may be heard over carotid, supraclavicular areas, brachial, and axillary arteries. Auscultation of the axillary fossa is particularly useful as bruits in this region are highly suggestive of large vessel vasculitis and are almost never due to arteriosclerosis.[26]

Examination of the abdomen may reveal abdominal aortic aneurysm which is usually palpable if 5 cm or larger.[27] Diastolic murmur of aortic regurgitation may be the first indication of a thoracic aortic aneurysm. Tissue gangrene, scalp necrosis, tongue ulcerations, or lingual infarction can be seen. Rarely, findings consistent with pleural and pericardial effusions have been reported.[28] A review of 83 patients identified 17 cases of giant cell arteritis presenting as a tumour-like lesion in the breast or ovary.[29]

Diagnostic criteria

Both this disease and its prolonged treatment with corticosteroids can be associated with serious sequelae. The American College of Rheumatology derived their diagnostic criteria from a retrospective study of 214 cases. The mean age at onset was 69 years and only 17 cases were older than 80 years. These criteria have sensitivity and specificity values of over 90%. However, these guidelines were developed as a research tool, and did not take into account occult or uncommon symptoms, neck pain, jaw claudication, and C-reactive protein.

Investigations

Laboratory findings are non-specific and reflect the inflammatory nature of giant cell arteritis. Acute-phase proteins are easily detected and useful markers of the disease. Elevated erythrocyte sedimentation rate (>50mm/hour) is common, but lower or even normal levels have been observed. Studies have shown that patients with lower erythrocyte sedimentation rate had less frequent systemic symptoms in comparison with patients with higher levels.[31] C-reactive protein is a more sensitive indicator of disease activity. A retrospective study looked at the erythrocyte sedimentation rate and C-reactive protein levels in patients with biopsy-proven giant cell arteritis and concluded that elevated erythrocyte sedimentation rate alone had a sensitivity of 76–86%, elevated C-reactive protein alone had a sensitivity of 97·5%, but when both were elevated, the sensitivity was 99%.[32] Presence of low erythrocyte sedimentation rate in the context of a patient with otherwise strong clinical suspicion of giant cell arteritis, should not delay treatment.

For a definite diagnosis, histological examination of an arterial biopsy is most useful. It helps to justify committing a patient to protracted systemic steroid therapy, in view of the possible serious complications of such long-term treatment, and to safeguard against possible litigation emerging from such complications. Temporal artery biopsy should be done as soon as possible, but withholding systemic therapy until after biopsy is not necessary.

Radiological investigations play an increasing part in the evaluation, particularly in those patients with large-vessel vasculitis and negative biopsy. Table 3 outlines the diagnostic approaches.

Management

Glucocorticoids

These steroids are the treatment of choice for giant cell arteritis as they effectively treat clinical manifestations and also have a role in preventing ischaemic complications. They do not seem to shorten the course of the disease and cannot reverse visual loss.[39] The aims of treatment are to limit further visual loss in the affected eye, prevent involvement of the fellow eye and suppress systemic disease activity.[40] An initial dose of 40–60 mg prednisolone is considered adequate for most cases.[1] Patients at high risk of developing ischaemic complications may need an initial dose of 1 mg/kg/day.[1] After response to initial therapy, the dose is tapered as per combination of clinical symptoms and inflammatory markers. Initial low dose or alternate-day dosing has been proposed, but concrete evidence of effectiveness is lacking. Treatment can last from 1–2 years to several years.

Glucocorticoid-sparing agents

Methotrexate, azathioprine and TNF-α inhibitors may be recommended in patients with longstanding, relapsing and steroid resistant cases, but have by no means replaced glucocorticoids.

Aspirin

In the absence of specific contraindications, low-dose aspirin is recommended for all patients because it effectively decreases the rate of cranial ischaemic events, including visual loss.[41] Vigilant follow up is essential as the course of the disease is variable; duration of treatment can be lengthy and, a substantial burden of medication side-effects exists. Awareness, monitoring, and prevention of side-effects is important for minimising risks among vulnerable adults. Boxes 2 and 3 highlight additional management considerations and long-term outcomes, respectively.

Conclusion

Giant cell arteritis is a clinical entity characterised by an often elusive presentation due to a wide and variable spectrum of signs and symptoms. No single laboratory investigation can confirm the diagnosis. Tissue biopsy, though rated as gold-standard by many can miss the diagnosis due to the presence of skip lesions.

Management in older patients may often be complicated by diagnostic uncertainty especially in those presenting with atypical symptoms, the presence of comorbid

Box 1: American College of Rheumatology criteria for the classification of giant cell arteritis[30]

- Development of symptoms or findings beginning at age 50 years or older
- Onset of new type of localised pain in the head
- Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
- Erythrocyte sedimentation rate of 50 mm/hour by Westergren method
- Abmornal artery biopsy sample showing vasculitis characterised by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

*For purposes of classification, at least 3 of these 5 criteria should be present. The presence of any 3 or more criteria yields a sensitivity of 93% and specificity of 91%

	Additional considerations
Laboratory tests	
Etythrocyte sedimentation rate	Raised, but can be lower or normal, even during flares
C-reactive protein	Raised: fairly sensitive, not affected by age or gender[28]
Interleukin-6	Raised: sensitive test, even during steroid treatment[33]
Normochromic normocytic anaemia	Negative predictor of ischaemic events [34]
Thrombocytosis	Well recognised
Leukocytosis	Well recognised
Elevated alkaline phosphatase	Seen in a third of patients, especially in biopsy-proven cases[28]
Hypoalbuminaemia	
Anticardioplipin antibodies	
von Willebrand factor and serum fibrinogen	No definitive association with ischaemic complications of giant cell arteritis
Imaging	
Chest X-ray	May reveal dilatation of the thoracic aorta
Echocardiography	Useful in evaluation of aortic valve ascending aortic disease
Ultrasonography	Hypoechoic halo seen around affected temporal arteries. Not used widely despite high specificity as sensitivity is very low and operator-dependent.[38]
CT angiography/ MR angiography	Particularly useful in assessing large vessel disease, especially in older people who present with claudication and/or pulselessness. Visualisation of aorta and other large arteries can demonstrate vascular abnormalities such as narrowing or irregularities.
Positron emission tomography/Gallium scinctigraphy	Uncertain diagnostic role
Temporal artery biopsy	
Clinical predictors of positive biopsy include arterial thickening, decreased pulse, scalp tenderness, and jaw claudication	High diagnostic yield
	Samples should be 2–3 cm long to improve yield[20]
	Contralateral side biopsy should be done only if the first biopsy is negative[35]
	Specimens may show arteritis for up to 2 weeks after treatment with steroids[36]
	False positive results are possible
	No definite criteria to distinguish between healed giant cell arteritis and senescent changes[37]

Table 3: Available diagnostic tests for giant cell arteritis

conditions, and increased frequency of adverse drug events. If the physician is not alert to the possibility of giant cell arteritis in older patients, common systemic symptoms may be misinterpreted. Giant cell arteritis is a treatable disorder. Prompt diagnosis and institution of treatment is crucial since many of the complications, including irreversible visual loss, are preventable.

We have no conflict of interest.

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Box 2: Additional management considerations

- A common schedule is to taper glucocorticoids and gradually reduce by 5 mg every 1–2 weeks until 10 mg. Thereafter, the dose can be reduced by 1 mg every 2–6 weeks, with close monitoring of clinical and laboratory markers.[1]
- Recognised complications of steroids include diabetes, hypertension, peptic ulcer disease, osteoporosis, dermatological effects, psychosis, proximal myopathy, and tuberculosis.[42]
- Glucocorticoids are known to reduce bone density. A recent study confirms poor prophylactic management of osteoporosis. Thus, appropriate osteoporosis prophylaxis should be considered for all patients on steroids.[43]
- Patients beginning therapy with long-term glucocorticoids need to be informed about side-effects and if necessary, advise lifestyle modification. Cigarette smoking and alcohol consumption both reduce bone density and advice to stop smoking and reduce alcohol consumption should be given.
- Regular blood pressure monitoring is important since glucocorticoids can induce or worsen hypertension.
- Glucose intolerance can develop secondary to glucocorticoid treatment and therefore, monitoring for diabetes mellitus and counselling regarding diet should be provided.
- Patients on low-dose aspirin and glucocorticoids should also take a proton pump inhibitor because of increased risk of gastrointestinal effects.[42]
- There is no clear evidence that influenza vaccination has a deleterious impact in these patients. Patients with giant cell arteritis should continue to receive annual inactivated influenza vaccinations.
- Ophthalmological assessment at baseline and regular intervals can be useful to monitor development or worsening of vision in patients with cataracts.
- An annual chest X-ray can be a useful screening approach in high-risk patients for detection of dilatation of thoracic aorta.[44]
- Annual transthoracic echocardiography can help to monitor valve disease.[44]
- Annual ultrasound screening for abdominal aneurysms in patients with giant cell arteritis is likely to be cost-effective, because of the increased risk of developing aneurysms.[44]

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Box 3: Long-term management of giant cell arteritis

1. Flare-ups

One of the most common causes of disease flares is tapering or lowering of glucocorticoid dose. Most flares are not accompanied by severe manifestations or raised inflammatory markers and are usually amenable to increased glucocorticoid dosage.[45,46]

Disease exacerbations unrelated to steroid therapy have also been reported.[1] A substantial proportion of patients may require long-term low-dose steroids.

2. Vision Loss

Vision loss, either partial or complete, in one or both eyes, is the most serious complication and is reported in up to 20% of patients. Glucocorticoid use is effective in preventing but not reversing vision loss.[24] Recovery of visual function in patients is very poor.[39]

Studies suggest certain factors to be predictive of ischaemic events that may lead to visual loss:[24,47]

- Absence of raised inflammatory markers
- Presence of systemic manifestations
- Older age at diagnosis
- Presence of thrombocytosis

No factors can entirely rule out the risk of blindness and, therefore, all patients must be encouraged to report any change in symptoms immediately.

3. Ischaemic events

Available evidence suggests no direct increase in mortality. However, the frequency of ischaemic events is increased, which may be fatal. This is more of a risk in patients whose disease activity is not sufficiently controlled.[48,51]

Large vessel involvement, including aneurysm formation and dissection, is life-threatening, usually occurring later in the course, and is often under-reported.

4. Glucocorticoid effects

Since treatment is often lengthy, vigilant follow-up of patients is essential. Studies have documented a significant effect of glucocorticoids on morbidity and, to a lesser extent, on mortality. Population studies suggest that up to 86% of treated patients develop side-effects.

Age and higher cumulative glucocorticoid dose were both predictors of adverse events.[49,50]

5. Prevalence of malignancies

Giant cell arteritis is not known to increase prevalence of malignancies or to be a paraneoplastic syndrome.[51]