

Large-Vessel Vasculitis

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ABSTRACT

The vasculitides affecting large and medium-sized vessels are heterogeneous. This group includes such disorders as giant cell arteritis, Takayasu's disease, and sarcoidosis. There are several challenges that may arise in the care of patients with these disorders.

Diagnosis may be elusive when initially evaluating patients with large-vessel vasculitis. Most serologic markers are not specific, and tissue biopsy is often impractical. We will present data emphasizing the most common disease manifestations, to aid in recognition of a clinical picture suggestive of large-vessel vasculitis. We will also focus on the more common pulmonary manifestations and minimize the inclusion of case reports, which may not reflect the usual course of disease.

Large cohort studies and randomized controlled trials to provide an evidence-based approach to therapy in these disorders are uncommon. We have included in this review discussion of those studies that we judged to be most rigorously conducted and clinically relevant. We provide guidelines for initial therapy, with caveats to assist in minimizing potential treatment-related complications and toxicities.

Although monitoring of disease activity is often difficult, this is a most crucial element in minimizing disease and treatment-associated morbidity and mortality.

KEYWORDS: Vasculitis, sarcoidosis, Takayasu's arteritis, giant cell arteritis

Objectives: Upon completion of this article, the reader should be familiar with the vascular features of sarcoidosis, giant cell arteritis, and Takayasu's arteritis.

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TAKAYASU'S ARTERITIS

Background

Takayasu's arteritis (TA) is a large-vessel vasculitis that preferentially affects the aorta and its primary branches. Chronic vascular inflammation results most frequently

in myointimal proliferation with stenosis, and less often attenuation of vessel wall integrity and aneurysm formation. Patients may present with signs and symptoms arising from tissue or organ ischemia, or have systemic and other manifestations including fever, arthralgias, myalgias, and weight loss. Additionally, some patients

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are asymptomatic, with disease first being detected when an absent pulse or unequal blood pressures between extremities are noted.

TA has been detected worldwide. It is most prevalent in the Far East. In Japan, ~150 new cases are reported per year,¹ whereas the reported incidence in Olmstead County, Minnesota, is only 2.6 cases per million population per year.² TA has a predilection for women of reproductive age, with onset of disease occurring most often in the third decade of life. Women are affected 8 to 10 times more frequently than men.

Pathogenesis

The etiology of TA is unknown. Although a genetic basis of disease has long been suspected, no single or multiple allelic association has been consistently identified in various ethnic groups. Potential infectious triggers have been closely studied. Mycobacterial pathogens have been suspect, but serologic and histological investigations have failed to consistently identify any association between infection and disease. Additionally, because of the female predominance of disease, hormonal factors have been examined. Investigations to date have not adequately evaluated mechanisms by which endocrine factors influence TA.

Mononuclear cells initiate and propagate vascular injury. This process begins with the entry of leukocytes into the vessel adventitia via the vasa vasorum. Subsequent chemokine and cytokine production affects both the intensity of the response and the types of cells recruited into the media and intima (e.g., macrophages, dendritic cells, and lymphocytes). Most often, vessel injury in TA leads to myointimal proliferation and stenosis. Aneurysm formation may also occur (< 25% of lesions) as a result of smooth muscle cell and elastic fiber destruction.

Although any elastic or muscular artery may be affected, primary branches of the aorta are affected in all patients. Stenoses generally develop slowly, resulting in the insidious onset of claudicatory or other ischemic symptoms. Proximal lesions are more common than distal lesions. The most commonly affected sites are the subclavian, innominate, common carotid, and vertebral arteries, as well as the aorta itself. Abdominal aortic stenosis is more common than stenosis of the thoracic aorta. These changes may coexist with abdominal branch vessel disease, causing visceral ischemia, hypertension (as a consequence of renal artery or suprarenal aortic stenosis), or lower extremity claudication.

Several classification systems for TA exist. Each focuses on specific sites of arterial involvement. One of the most widely accepted systems³ subdivides patients into four groups based on abnormalities in the following sites:

1. Type I: aortic arch and branch vessel involvement
2. Type II: descending, thoracic, and abdominal aorta and/or its branches
3. Type III: combination of Types I and II
4. Type IV: Type I-III, plus pulmonary artery involvement

The majority of patients meet criteria for Type III.

Clinical Features

The most common clinical finding in TA is vascular bruits, which are found in up to 94% of patients.² The most common sites for bruits are in the regions of the most commonly involved vessels (*vide supra*). Pulse or blood pressure discrepancies when comparing measurements between right and left upper or lower extremities are present in 80 to 96% of patients^{4,5} (Fig. 1).

Some of the most devastating manifestations of TA occur as a result of central nervous system involvement. Lesions in the carotid or vertebral arteries can lead to transient ischemic attacks, blindness, amaurosis fugax, or stroke. Symptoms of cerebrovascular insufficiency are nonspecific and include dizziness, lightheadedness, near-syncope, orthostasis, and vertigo.^{6,7} Visual compromise may result from stenoses within the ophthalmologic branches of the internal carotid circulation leading to decreased retinal perfusion (Takayasu's retinopathy). Although seen in up to 25% of Japanese patients, this is rarely reported in Western series.⁸ Hypertensive retinopathy, glaucoma, cataracts, and vitreous hemorrhages are more common etiologies of vision loss in TA.

TA leads to aortic insufficiency in 17 to 55% of patients as a result of aortic root dilatation.^{9,10} Other cardiac manifestations include arrhythmias, cardiomyopathy, and congestive heart failure. Coronary vasculitis



Figure 1 Takayasu's arteritis. Angiography demonstrating bilateral subclavian artery stenosis (SC) with left common carotid graft (G) to distal left subclavian artery and right common carotid artery dilatation (RCC). Note subsequent stenosis of the left subclavian artery, rendering the graft ineffective.

Table 1 Prevalence of Pulmonary Arterial Involvement in Takayasu's Arteritis

Author (ref #)	Cases	Frequency of Involvement (%)	Imaging
Sharma et al ^{9a}	44	14.3	IV-DSA
Yamada et al ^{9b}	30	50	MRA
Sheikhzadeh et al ⁹	78	16	CDA
Vanoli et al ^{9c}	15	60	SPET
Ogawa et al ^{9d}	57	56	SPET

IV-DSA, intravenous digital subtraction angiography; CDA, catheter directed angiography; SPET, single photon emission tomography with scintigraphy; MRA, magnetic resonance angiography.

has been reported in 7.2% of 78 patients.¹⁰ Pericarditis and myocarditis are rare in TA.

Pulmonary abnormalities of TA are varied and are often asymptomatic. Pulmonary vascular involvement, initially thought to be uncommon, has been identified with increasing frequency by a variety of imaging techniques (Table 1^{9,9a-d}) (Fig. 2). There is no clear predilection for particular pulmonary arterial branches or lung zones, but, as in the systemic circulation, larger vessels are favored. Pulmonary vascular involvement in both autopsy studies and imaging studies is documented in the majority as stenosis, but case reports of dilatation or aneurysms exist. Lie described the presence of isolated unilateral giant cell pulmonary arteritis in five patients (age range 25–66), suggesting that this may represent a variant of TA.¹¹ Although the histopathology in these patients may be similar to the arterial lesions in patients meeting the American College of Rheumatology (ACR) criteria for TA, the prognosis and appropriate treatment for this disease phenotype are less clear than for TA.

The prevalence of associated pulmonary hypertension in TA has not been examined extensively, but one study of 22 patients with TA documented elevated pulmonary artery pressures (> 30 mmHg) by right heart

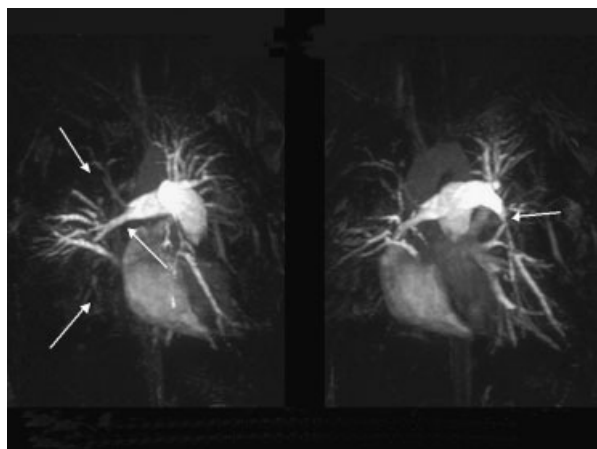


Figure 2 Takayasu's arteritis. Magnetic resonance imaging demonstrates decreased blood flow to the right upper and lower lung fields and a focal stenotic lesion of the left inferior branch of the pulmonary artery.

catheterization in 73% of patients.¹² The appearance of arterial involvement on angiography may mimic that of thromboembolic disease. Case reports of pleural effusion, interstitial pneumonitis, and massive hemoptysis have been documented as complications of TA. However, review of these case reports finds insufficient data to conclude that these manifestations are solely a result of active TA. The prudent approach to a TA patient with pulmonary disease is to also evaluate for other etiologies, such as infection or thromboembolic disease. Symptoms associated with pulmonary involvement in TA are nonspecific and may include chest pain, cough, dyspnea, or hemoptysis.

Visceral artery involvement is often detected on angiography, occurring in 18 to 66% of cases.^{2,13} Insidious progressive vessel stenosis may allow for development of adequate collateral circulation. Many lesions may not cause gastrointestinal ischemic symptoms. Patients should undergo vessel restoration procedures for mesenteric ischemia in the setting of documented persistent intestinal angina or acute visceral infarction. Renal artery stenosis occurs in 28 to 76% of patients, and frequently results in hypertension^{2,9,14} (Table 2^{2,4,13,14a-d}). The presence of extremity stenoses often masks the onset of central (aortic) hypertension. Hypertension that is undetected or inadequately treated may lead to significant morbidity and mortality.

Diagnosis

The diagnosis of TA is made in the setting of a compatible clinical profile, accompanied by visualization of arterial vascular lesions. Catheter-directed angiography is the gold standard of vascular imaging in TA and should be performed in all patients at initial presentation. Central aortic pressure and gradients across stenoses should be measured to assess hemodynamic significance and to determine whether peripheral blood pressure measurements by cuff accurately reflect central aortic pressure. Other imaging modalities [e.g., computed tomography (CT) or magnetic resonance angiography (MRA)] may be useful in TA for monitoring disease progression. However, there are no imaging techniques currently available to accurately assess vessel wall inflammation. MR and CT imaging are only capable of assessing the luminal diameter and wall thickness within ~1 mm of reliability. This may be useful to detect progression of existing lesions or the appearance of new lesions, but is not an ideal means of assessing disease activity. MR imaging utilizing T2-weighted images and STIR (slow time inversion recovery) imaging has been studied in TA for monitoring disease activity by detection of extracellular fluid (tissue edema). Although a high frequency of vessel wall edema was found in patients with clinically active TA (94% of studies), vessel edema was also detected in over half of studies in

Table 2 Prevalence of Hypertension and Renal Artery Involvement in Takayasu's Arteritis

Author (ref #)	Country	Patients (#)	Hypertension (%)	Renal Artery Stenosis (%)
Lupi-Herrera et al ⁴	Mexico	107	72	67
Rose and Sinclair ^{14a}	S. Africa	16	87	31
Kerr et al ¹³	U.S.	60	33	38
Hall et al ²	U.S.	32	31	76
Lagneau and Michel ^{14b}	France	35	60	60
Chugh et al ^{14c}	India	125	92	88
Sharma et al ^{14d}	India	72	61	62

patients with inactive or uncertain disease activity status.¹⁵ Most importantly, the presence of vessel wall edema did not consistently correlate with the development of new anatomic lesions on subsequent studies. Fluorine-18 fluorodeoxyglucose positron emission tomography (18 FDG PET) imaging in the detection and monitoring of vascular inflammation is currently under study. Data from several small studies suggest that this technique may be helpful in detecting and monitoring vascular inflammation associated with large-vessel vasculitis.¹⁶ However, uptake is also noted in vessels with atherosclerosis, which may limit the utility of this technique.

There are significant limitations in serologic or clinical detection of disease activity. Acute phase reactants may be normal in patients with active disease, and patients who appear clinically to have quiescent disease may manifest new lesions on serial imaging studies. This is illustrated further in a study examining surgical pathology in patients requiring vascular intervention while appearing to be in clinical remission. Active vasculitis may be found in about half of such specimens.¹⁷

Treatment

Most patients with TA require therapy. Up to 20% may have a monophasic disease course, without progression or recurrence after the initial event. The remainder will require treatment to preserve vessel integrity and prevent involvement of other vascular territories. Treatment should be initiated when patients have active disease, which may be difficult to determine. Kerr et al¹³ define active disease as any two or more of the following:

1. New or worsening signs and symptoms of vascular ischemia or inflammation
2. Elevated sedimentation rate
3. Typical angiographic features
4. Systemic symptoms not attributable to another disease

These findings are useful when present, but their absence does not ensure that disease is inactive.

Glucocorticoids (GC) are first-line therapy in TA. Over half of all patients will attain remission with steroid therapy, but half of these patients will relapse when GC are tapered. Additional disease-modifying agents may aid in disease control in patients with GC-resistant disease, or when patients are unable to taper prednisone below a daily dose of 10 mg without relapse. In a National Institutes of Health (NIH) study, low-dose methotrexate (MTX) was demonstrated to be efficacious in 13/16 patients with GC-dependent or resistant disease.¹⁸ Nearly half of these patients were able to discontinue steroid therapy during the follow-up period. There are conflicting data on the use of mycophenolate mofetil for TA; in our own experience, this agent has provided little additional benefit. If MTX does not allow for successful GC tapering, and disease is severe, cyclophosphamide should be considered. Cyclophosphamide administered with GC was demonstrated by Shelhamer et al to induce remission in 4/6 patients with steroid-resistant disease.¹⁹ We recommend initiation of cyclophosphamide therapy with a dose of 1 mg/kg/day, with treatment for no longer than 6 months to minimize associated toxicities. A pilot study utilizing anti-tumor necrosis factor (TNF) therapy in TA demonstrated complete sustained remission in 10/15 and partial remission in 4/15 patients.²⁰

Treatment of hypertension is an important aspect in the care of patients with TA. Many associated disease-related complications are a direct result of undetected or inadequately treated hypertension. Hypertension often results from renal artery stenosis, which is often amenable to surgical correction. Medical therapy of hypertension should be initiated cautiously. Rapid lowering of blood pressure in the setting of stenoses of vessels supplying critical organs may result in ischemia and irreversible end organ damage. In patients with stenoses affecting all extremities, leaving no means of accurate peripheral blood pressure measurement, surgical correction to provide one limb as a reliable reference to central aortic pressure should be considered to assess blood pressure control. An individualized approach should be taken in each patient requiring surgical intervention, based upon the nature and distribution of their vascular

lesions. Ideally, surgery should be undertaken during a period of disease inactivity. Intervention should be considered in the setting of hypertension resulting from renal artery stenosis, or symptomatic cerebrovascular, myocardial, or visceral ischemia, and extremity claudication that severely limits normal activities. Aortic insufficiency resulting from enlarging aortic root aneurysms may lead to hemodynamically significant aortic regurgitation, congestive heart failure, or cardiac ischemia from inadequate coronary artery filling. When aortic root enlargement necessitates surgical reconstruction, valve replacement is usually also required.

Renal artery stenosis may be successfully treated by percutaneous angioplasty, with initial vessel patency reported as high as 81%.²¹ However, we have found that sustained patency of stenoses in TA, treated either by angioplasty or angioplasty with stenting, is difficult to attain.²² The diffuse vascular thickening of TA is less amenable to dilatation than a localized plaque. Currently we do not recommend stenting in patients able to undergo a bypass procedure. However, with the advent of drug-eluting stents, this may not be the case in the future. Studies of these novel devices in TA are needed to determine their efficacy.

Bypass grafting is the mainstay of therapy for all accessible lesions, with an important caveat: arteries prone to involvement by TA should not be used for the origin of anastomoses. For example, when bypass is performed for carotid artery stenosis, the subclavian artery should not be used as the graft origin. Because the subclavian artery will become stenotic in over 90% of patients, the probability of graft loss in this setting is unacceptably high.

Although TA patients are generally young, disease-related complications may increase their surgical risk. A retrospective review following 106 consecutive patients with TA after operative intervention documented 12 perioperative deaths (11.3%), mainly occurring as a result of cardiovascular complications.²³ However, other series document perioperative mortality as low as 3%.²⁴ Surgical outcomes may be impacted by the experience of the surgical team and medical center in caring for patients with TA.

Potential Pitfalls

1. It is important to realize that progression of existing vascular lesions may not indicate disease activity. Turbulent flow from vessel damage, combined with other factors such as hypertension, hyperlipidemia, smoking, and aging, will promote atherogenesis even when disease is quiescent. The appearance of new lesions in new vascular territories is the most definitive evidence of disease activity. Systemic signs and symptoms, and/or elevation of acute phase reactants,

may also signal active disease, but these are less specific.

2. TA may remain active in asymptomatic patients, even when systemic signs and symptoms were part of the initial presentation. Sequential imaging is necessary to determine response to treatment and assess disease progression.
3. New signs and symptoms of illness should receive the same considerations as they would in patients without TA. They may indicate an unrelated comorbidity. Additionally, the physician should remain mindful of the risks and potential toxicities of therapeutic interventions utilized. For example, the presence of new pulmonary infiltrates could result from opportunistic infection, congestive heart failure, or drug-associated pneumonitis rather than a disease-associated manifestation.

GIANT CELL ARTERITIS

Background

Giant cell arteritis (GCA) (temporal arteritis) is a vasculitis of unknown etiology that primarily affects medium- and large-sized arteries. GCA most often affects the extracranial branches of the aortic arch but can also involve the aorta and its other branches. The prevalence of GCA is highest in patients over the age of 50, with a mean age of onset of ~74 years. GCA occurs more often in Caucasians, especially those of Northern European origin. Women are affected at least twice as often as men.

GCA may have an insidious or acute onset. Presentation is highly variable, with some patients manifesting with a predominance of constitutional symptoms, whereas others have symptoms directly resulting from vessel injury such as headache, masseter muscle or extremity claudication, or visual aberrancy. Initial disease manifestations are provided in Table 3.^{25,25a,25b}

Pathogenesis

The inciting event in GCA is unknown. It has been proposed that the disease process begins with an antigen-specific response within the walls of target arteries.²⁶ It is postulated that antigen recognition by T cells and antigen-presenting cells within the adventitia leads to the production of inflammatory cytokines and chemokines, resulting in enhanced influx of mononuclear cells. In addition to dendritic cell and macrophage activation, interferon-gamma and TNF from Th1 lymphocytes also participate in generation of giant cells and granuloma formation.²⁷ Giant cells and macrophages produce factors such as platelet-derived growth factors and vascular endothelial growth factor, which stimulate neoangiogenesis in normally avascular regions of the

Table 3 Giant Cell Arteritis: Clinical Features (Frequency %)

Clinical Features	Hunder ²⁷ (n = 94)	Liozon ³⁰ (n = 147)	Gonzalez-Gay ^{25a} (n = 239)	Chevalet ^{25b} (n = 164)	Hoffman ^{38f} (n = 98)
Headache	77	NS	83	67	93
Temporal artery abnormality	53	55	72	21	NS
Jaw pain/ Claudication	51	38	39	16	60
Constitutional symptoms	48	65	70	NS	NS
Polymyalgia rheumatica	34	27	47	49	55
Fever	27	NS	11	46	5
Diplopia	12	NS	7	NS	NS
Amaurosis	5	NS	17	NS	NS
Blindness	13	13	14	NS	18
Stroke	NS	NS	3.5	NS	0

NS, not stated.

Modified from Hoffman GS. Treatment of giant cell arteritis: where we have been and why we must move on. *Cleveland Clinic J Med* 2002; 69(suppl 2):S11-117-120.

vessel wall. The proliferation of myofibroblasts and deposition of matrix in the vessel intima leads to hyperplasia and obstruction, whereas matrix metalloproteinases allow entry of inflammatory cells into the media with resultant destruction of smooth muscle and elastic membranes.²⁸

Clinical Features

The most common symptom of GCA is headache, which occurs in at least two thirds of patients. It may be mild or severe, temporal, frontal, occipital, or generalized. Often it is reported as being unlike any previously experienced. Scalp tenderness may accompany headache, is often detected over the temporal regions, but can affect any part of the head.

One of the most potentially devastating manifestations of GCA is visual loss, resulting from optic nerve or tract ischemia from involvement of the ophthalmic or posterior ciliary arteries. Amaurosis fugax is the most common predictor of permanent visual loss. Visual impairment is most often unilateral. However, in the absence of adequate treatment, it may evolve to bilateral blindness. Fourteen to 20% of cases may present with visual loss, and up to 28% of patients may develop visual loss during the course of illness.^{29,30} Less common neurological manifestations include TIA and stroke.

The muscles of mastication are the most common site of intermittent ischemic muscle pain. Nearly half of GCA patients report jaw claudication. However, involvement of other primary aortic branches, such as those supplying the upper extremities, may result in limb claudication and fatigue (Fig. 3).

Muscle discomfort may arise from polymyalgia rheumatica (PMR), which may manifest before, after, or at the time GCA is diagnosed.³¹ Symptoms compatible with PMR are noted in nearly half of all patients with GCA. Conversely, patients with PMR are at higher risk

for developing GCA, with GCA occurring in 0 to 80% of cases.³²

An often underappreciated complication of GCA is the development of aortitis, which may result in aortic aneurysm and dissection. Aortitis may occur at disease onset, or any time following diagnosis. Dissection or aneurysm generally present later in the disease course. An autopsy series that examined sections of the aorta and its primary branches in 14 patients (13 with GCA, one with TA) revealed widespread changes throughout the aorta and branch vessels.³³ These findings support our suspicion that large-vessel involvement usually occurs in GCA patients and is often unrecognized.

Pulmonary vascular or parenchymal manifestations of GCA are documented mainly in case reports. Mononuclear cell infiltration, with giant cell formation within the large pulmonary arteries, has been documented in patients both with and without a clinical diagnosis of GCA.^{34,35} When detected as an isolated finding, it is not clear that this is part of the spectrum of giant cell arteritis.

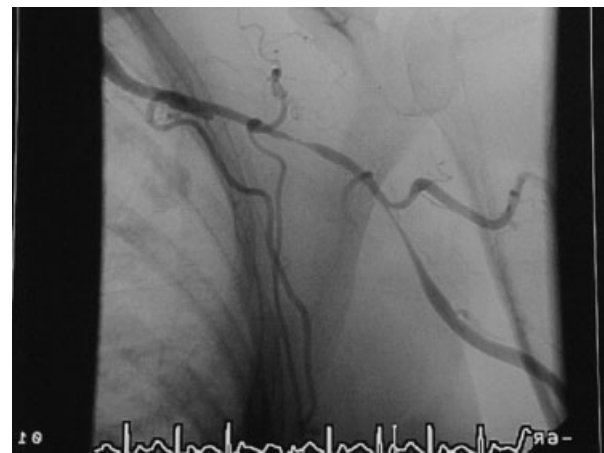


Figure 3 Giant cell arteritis. Angiography demonstrating subclavian and more distal axillary artery stenosis.

Review of reports of pulmonary parenchymal nodules, interstitial infiltrates, alveolar hemorrhage, and pleural effusions in GCA leaves questions about whether these findings were in fact not due to comorbidities (such as infection, thrombosis, or neoplasm) or if another form of vasculitis was present. Therefore, pulmonary disease occurring in the setting of GCA should be fully evaluated and not assumed to be due to GCA.

Larsen et al³⁶ reported upper respiratory tract symptoms in up to 9% of patients. In 4% of these patients, these symptoms were so severe as to be the presenting complaint. Patients noted cough, sore throat, or hoarseness. These symptoms rapidly resolved after therapy was initiated. The features were postulated to occur as a result of ischemia or inflammation of the affected tissues.³¹ Histopathologic correlation was not available.

Diagnosis

A diagnosis of GCA should be considered in patients over the age of 50 who present with a new or uncharacteristic headache, or the acute onset of visual impairment, in the setting of systemic inflammation that cannot be attributed to other causes. Patients must be carefully examined for other signs of vascular involvement, including auscultation for bruits and cardiac murmurs.

The gold standard for diagnosis remains tissue biopsy, most frequently of the temporal artery. The finding of aortitis on an aortic specimen may also identify the presence of disease, even in a patient without the classic clinical presentation. Vessel histopathology reveals wall infiltration by lymphocytes and macrophages, with giant cells present in ~50% of specimens.^{28,37} Intimal thickening and elastic membrane fragmentation are also characteristic. Biopsy should be performed as soon as possible after the diagnosis is suspect. Arrangements for biopsy should not delay the onset of therapy in patients with a high suspicion of GCA. Because of the presence of skip lesions in the vessels involved in GCA, a negative biopsy does not ensure the absence of disease.

Other diagnostic modalities, such as ultrasound, have been studied as a potential means of detecting GCA noninvasively. Salvarani et al demonstrated the predictive value of a positive ultrasound study to be less than that of finding a temporal artery abnormality on physical examination (tenderness or decreased or absent pulse).³⁸ Angiography may be useful when involvement of the aorta and its primary branches is suspected. Angiography is also helpful in delineating the severity of concurrent atherosclerosis in this elderly population. New techniques utilizing the combined approach of PET with either MR or CT imaging to detect vessel inflammation are under study.

Treatment

GC are the mainstay of therapy in GCA. When the diagnosis is highly likely, based on clinical and laboratory data, treatment should be started immediately. Although symptoms may rapidly improve, arterial inflammatory changes lag behind, allowing for detection of disease on biopsy even after several days or even weeks of therapy. Most authorities recommend initial therapy with 40 to 60 mg of prednisone daily, administered in a single or divided dose. Tapering of steroids may be initiated after 2 to 4 weeks of therapy, provided that adequate symptomatic response has occurred. Serologic monitoring should be performed at about monthly intervals, with patients assessed regularly for relapse. GC may be reduced every 1 to 2 weeks by ~10% of the daily dose, as long as laboratory parameters remain normal and patients remain asymptomatic. As the daily dose reaches 10 to 15 mg/day, it may be advantageous to slow tapering to 1 mg every 2 to 4 weeks, as tolerated. Unfortunately, adjunctive disease-modifying agents have not demonstrated significant utility in allowing for more rapid reduction of GC therapy in patients with relapsing disease. Most patients are unable to sustain steroid-free disease remission (Table 4^{38a-f}). A trial examining the use of anti-TNF therapy in GCA is under way. As with all patients who require chronic GC therapy, those with GCA should have a baseline bone density assessment and therapy for prevention or treatment of osteoporosis.

In addition, it is important to realize that aortic and branch vessel involvement may occur at any time in the disease course, even in the absence of other symptoms. Patients should be evaluated regularly even during apparent remission, with careful history and examination focusing on signs and symptoms suggestive of large-vessel involvement.

Potential Pitfalls

1. Aortitis may occur or progress even in the absence of clinical signs or symptoms of GCA. Regular examination focused on cardiovascular signs and symptoms, and monitoring of acute phase reactants are

Table 4 Relapsing Disease in Giant Cell Arteritis

Author	Patients (#)	Relapsing Disease (%)	Time Followed
Proven et al ^{38a}	120	48	2–22 months
Hachulla et al ^{38b}	133	62	25 months
Liozon et al ^{38c}	58	47	34 months
Andersson et al ^{38d}	90	50	108–192 months
Jover et al ^{38e}	42	64	24 months
Hoffman et al ^{38f}	98	83	12 months

crucial, even if clinically apparent sustained remission is attained.

2. Patients with PMR may develop GCA at any time during their disease course. Any new headache or visual disturbance should be considered a potential manifestation of GCA in these patients. Therapy should be adjusted accordingly until further investigation is performed.
3. Other forms of systemic vasculitis may involve the temporal artery. Although this is uncommon, polyarteritis nodosa, microscopic polyangiitis, or Wegener's granulomatosis may result in an abnormal temporal artery biopsy. These disorders can usually be differentiated from GCA by the overall clinical picture.

SARCOIDOSIS

Background

Sarcoidosis is an idiopathic systemic inflammatory disease characterized by the presence of noncaseating granulomas in affected organs and tissues. Although all systems are vulnerable to disease, the most frequently affected include the lymph nodes, lungs, liver, skin, and eyes. The nature of disease onset varies from acute to insidious. Signs and symptoms may be systemic and nonspecific, or related to the organ system(s) involved. Sarcoidosis may have a benign, self-limiting course or evolve into a chronic illness that may be life threatening.

Sarcoidosis occurs worldwide. It may occur at any age but is most frequently diagnosed in the third and fourth decades of life.³⁹ Common signs and symptoms of sarcoidosis include fatigue, malaise, cough, dyspnea, and chest pain. Lofgren's syndrome, the triad of hilar lymphadenopathy, erythema nodosum, and arthralgias, is an acute form of sarcoidosis. The great majority of patients with this acute onset profile attain spontaneous and sustained remission. However, up to 16% may have persistent disease.⁴⁰

Pathogenesis

The presence of granulomas has been suggested to be a reaction to a yet to be identified infectious agent(s). The interaction of CD4+ T helper cells and macrophages induce cytokine production and release, which leads to giant cell and granuloma formation. Sarcoid granulomas are characterized by no or minimal necrosis and no caseation, except in necrotizing sarcoid granulomatosis. Lesions often contain giant cells with cytoplasmic inclusions.

Clinical Features

Musculoskeletal involvement in sarcoidosis is highly diverse. Granulomas may be present in muscles or bones,

and even in the synovium. Muscle involvement may be associated with creatinine kinase elevation and myopathy. Lupus pernio, nodular violaceous cutaneous lesions, may be associated with bony involvement. Joint involvement in acute sarcoidosis most often affects the knee or ankle, with periarticular swelling being more frequent than synovitis, although both may occur simultaneously. Sarcoid arthritis may be mild and transient, or severe and persistent. In the latter case, destructive changes may mimic severe rheumatoid arthritis.

Cardiac involvement by sarcoidosis is diagnosed in only ~5% of patients. Autopsy studies suggest that myocardial involvement occurs in up to 27%.^{41,42} Fibrogranulomatous inflammation and scarring may result in conduction block and dysrhythmias, or congestive heart failure from decreased contractile function or impaired ventricular relaxation. Sudden death may occur from conduction block or ventricular tachyarrhythmias.

Sarcoidosis may lead to vascular compromise by two separate means: extrinsic vascular compression by enlarged lymph nodes, or by inflammatory vascular disease. Although pulmonary vascular involvement is a common facet of pulmonary sarcoidosis, extrapulmonary vasculitis is rare, with there being fewer than 100 cases reported in the English literature.⁴³ Vasculitis in sarcoidosis may occur at the time of diagnosis or present many years into the disease course.

Sarcoid small vessel vasculitis results in a variety of skin manifestations including erythema nodosum, scar infiltration, palpable purpura, nodular or papular lesions, bullous lesions, extremity ulcerations, and polycyclic erythematous rashes.⁴⁴ The synovium may also be a site of small-vessel vasculitis.

Sarcoid medium- and large-vessel vasculitis is rare. About 20 cases have been reported in the English literature. Aortic disease may manifest as wall thickening, stenosis, aneurysm formation, or dissection (Fig. 4).

Inflammation of other large vessels frequently occurs with aortic disease, including the pulmonary,



Figure 4 Magnetic resonance angiography. Sarcoidosis with severe stenosis of the abdominal aorta.

Table 5 Chest Radiograph Findings in Sarcoidosis

Finding	Frequency (%)
Left or right hilar adenopathy	70–90
Left paratracheal adenopathy	60–80
Reticulonodular abnormalities	60–70
Acinar abnormalities	10–20
Large nodules	< 5
Cavitary lesions	< 5
Pleural effusion	< 5
Atelectasis	< 1
Cardiomegaly	< 1

(From Crystal.⁴⁵)

subclavian, coronary, renal, or iliac arteries. Signs and symptoms associated with medium- and large-vessel vasculitis include extremity claudication, abdominal pain (mesenteric arteritis), hypertension (associated with renal artery stenosis in 3/7 documented cases), and carotidynia.⁴⁴ Associated morbidities with large- or medium-vessel disease include renal failure, digital ischemia, stroke, and limb gangrene. In some instances sarcoid vasculopathy can mimic Takayasu's arteritis.

Pulmonary manifestations of sarcoidosis are common. About 90% of patients have an abnormal chest radiograph during their disease course (Table 5).⁴⁵ Nearly half of patients will have persistent pulmonary abnormalities, whereas up to 15% develop progressive fibrosis. Patients with adenopathy alone are often asymptomatic. Interstitial disease may manifest with dry cough or dyspnea, typically worse with exertion.

Pulmonary vascular involvement is common in necrotizing sarcoid granulomatosis (NSG). NSG usually involves small- and medium-sized muscular arteries and veins. Although considered a variant of sarcoidosis by some, important differences exist. The presentation and radiological findings of NSG may mirror those of sarcoidosis. However, patients rarely have hilar adenopathy.⁴⁶ The histopathology of NSG includes granulomatous pneumonitis, "sarcoidlike" granulomas, and vasculitis. Widespread regions of coagulative necrosis are key to the histological differentiation of NSG from sarcoidosis.

Diagnosis

The diagnosis of sarcoidosis is best supported by the presence of noncaseating granulomas on biopsy combined with a compatible clinical picture, when all other potential causes of granulomatous disease are eliminated. Although leukopenia, anemia, hypercalcemia, and elevation of acute phase reactants are often present, they are nonspecific and not a reliable means of supporting or refuting a diagnosis of sarcoidosis. Angiotensin converting enzyme (ACE) levels may parallel disease activity

Table 6 Angiotensin Converting Enzyme Levels in Granulomatous Diseases Other Than Sarcoidosis

Disease	Patients (#)	Mean Value (nmol/min/mL)	Elevated Values (%)
Sarcoidosis (chronic)	66	50	50
Active pulmonary tuberculosis	80	34	10
Primary biliary cirrhosis	31	44	16
Hepatic granulomatous disease (unspecified)	8	41	16
Hodgkin's disease	5	47	40
Inflammatory bowel disease	26	31	0
Leprosy	20	20	0

(From Studdy et al.⁴⁷)

but are increased in other granulomatous diseases, limiting their diagnostic use (Table 6).⁴⁷ Elevation of ACE levels is noted in 50 to 80% of patients with active sarcoidosis.^{46,47}

Cardiac involvement should be suspected in patients with abnormal electrocardiographic findings. Two-dimensional echocardiography may reveal systolic or diastolic dysfunction, but these findings are nonspecific. Endomyocardial biopsy is the only definitive means of diagnosing cardiac sarcoidosis. Because tissue involvement is not uniform, sampling limitations may not identify all cases. Cardiac MR and FDG PET imaging have been purported to detect abnormal areas of the myocardium, felt to be consistent with sarcoid infiltration. However, the small numbers of patients studied and absence of histopathologic correlation limit the utility of conclusions from those reports.^{41,48}

The diagnosis of small-vessel vasculitis in sarcoidosis may be made by biopsy. Granulomas may be found in either or both tissue parenchyma and vessels. Large-vessel involvement is best assessed by arteriography.

Treatment

The treatment of sarcoidosis needs to be tailored to address individual disease manifestations. Patients with mild stable disease with minimal symptoms may never require therapy. Progressive disease or critical organ involvement may respond to treatment with corticosteroids. The severity of involvement, organ distribution, and rate of progression will determine the choice of initial corticosteroid dose and rate of taper. Hydroxychloroquine may be helpful in managing cutaneous disease. Limited data examining the adjunctive use of MTX, cyclosporine, and azathioprine suggest some benefit in disease management. A trial of etanercept, an anti-TNF agent, in patients with stage II or III progressive pulmonary sarcoidosis, was terminated early

due to excessive numbers of treatment failures.⁴⁹ Further studies utilizing this class of agents are ongoing.

Large-vessel vasculitis associated with sarcoidosis requires aggressive immunosuppression. It has been recognized in the few cases reported that inadequate treatment is associated with a high mortality rate.⁵⁰ Failure to achieve a rapid response from high-dose corticosteroid therapy mandates the addition of a cytotoxic agent.

Potential Pitfall

Sarcoidosis should be a diagnosis of exclusion. Other disorders, such as fungal infections or malignancy, may be clinically indistinguishable. Sarcoid, GCA, TA, or Wegener's granulomatosis may all affect large vessels. Common characteristics of each disease allow distinction to be made in almost all cases.

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