Symptomatic Lower Extremity Vasculitis in Giant Cell Arteritis: A Case Series

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ABSTRACT. ***Objective.*** To describe the clinical features and outcomes of 19 patients with giant cell arteritis (GCA) and symptomatic lower extremity (LE) vasculitis.

Methods. We reviewed medical records of all patients diagnosed with GCA and symptomatic LE involvement between January 1, 1983, and June 30, 2007, for clinical features, laboratory and radiographic findings, and outcomes.

Results. From 6212 people evaluated for GCA at our institution between 1983 and 2007, we identified 19 cases of GCA with LE vasculitis, all women. Mean age at GCA diagnosis was 70 years (± standard deviation 7.99). Sixteen patients (84.2%) had LE symptoms preceding the diagnosis of GCA, median interval 3 months (range 1–48). Three patients (15.8%) had GCA prior to developing LE claudication, median interval 16 months (range 9–34). Cranial symptoms were absent in 42.1%. No patient had permanent visual loss. Erythrocyte sedimentation rate (ESR) was elevated in 16 patients (84.2%), with median ESR 42.5 mm/h (range 8–103). Imaging studies revealed stenotic, occlusive, or aneurysmal disease that was frequently bilateral and consistent with vasculitis. The superficial femoral arteries were most commonly affected. Five patients (26.3%) had upper extremity involvement. Hypertension was the most common cardiovascular risk factor. All patients received glucocorticoid therapy, with clinical improvement in 15 patients (79%). Median length of followup was 41 months (range 11–180 mo). Five patients (26.3%) underwent LE revascularization surgery. Two patients required LE amputation and 1 patient underwent toe amputation. Five patients received additional immunosuppressive therapy.

Conclusion. Symptomatic LE vasculitis from GCA is rare. Patients typically present with rapidly progressive LE claudication and elevated inflammatory markers, while cranial symptoms may be absent. GCA with LE involvement is associated with significant morbidity; prompt diagnosis and treatment is essential. (J Rheumatol First Release Sept 15 2009; doi:10.3899/jrheum.090269)

Key Indexing Terms:
VASCULITIS
GIANT CELL ARTERITIS
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INTERMITTENT CLAUDICATION

Giant cell arteritis (GCA) is a granulomatous vasculitis of medium and large-size arteries. It is the most common vasculitis in individuals over the age of 50 years, with an estimated annual incidence of 15–33 cases per 100,000 persons in populations with predominantly Northern European ancestry[1]. Large-vessel involvement of the aorta and its primary and secondary branches is a well known complication of GCA[2]. Although the lower extremity (LE) arteries can be involved in GCA, symptomatic LE involvement is rare. In a population-based cohort study of large-artery complications from GCA, 1 patient developed iliac and femoral stenosis in a cohort of 168 patients over a 50-year study period[3]. Recognition of this unusual but known complication of GCA is important since early diagnosis and therapy could potentially affect outcomes. In an earlier clinical case series of 8 patients with LE arterial involvement from GCA, 1 patient required amputation and 3 others underwent a bypass procedure, in some cases, because the diagnosis of GCA was not suspected[4]. We reviewed all cases of LE claudication associated with GCA evaluated at our institution to describe the clinical features and outcomes of these patients.

MATERIALS AND METHODS

Study design. This was a retrospective case series of all patients with GCA and LE vasculitis seen at Mayo Clinic, Rochester, between January 1, 1983, and June 30, 2007. All patients provided authorization for review of their medical records. The Institutional Review Board approved the study.

Case retrieval. Using Hospital International Classification of Disease Adaptation (HICDA) codes for GCA or temporal arteritis in combination with LE claudication, claudication, intermittent claudication, peripheral arterial disease, or peripheral vascular disease, all patients with the above diagnoses evaluated at Mayo Clinic from January 1, 1983, to June 30, 2007, were identified. Only patients with symptomatic LE vasculitis from GCA were included.

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Case definitions. GCA was diagnosed by positive tissue biopsy and/or by large-vessel imaging [conventional angiography, computed tomography angiography (CTA) or magnetic resonance angiography (MRA)]. LE claudication was defined as reproducible discomfort of any muscle group in the LE induced by activity and alleviated by rest. LE involvement from GCA was defined as symptomatic claudication of the LE with findings of LE arterial disease as diagnosed by noninvasive arterial Doppler studies (ankle-brachial index < 0.9), conventional angiogram, CTA, or MRA. Only cases in which the interpreting radiologist concluded that the imaging studies were consistent with vasculitis based on findings such as long tapered stenoses and/or vessel thickening were included.

Exclusion criteria. Patients were excluded if they did not have symptoms of claudication, if there were no studies documenting LE disease, or if the symptoms of LE claudication were attributed to atherosclerosis by the treating physician or the radiologist interpreting the imaging findings. Patients with imaging studies showing changes of atherosclerosis such as focal stenosis, plaque, or calcification were excluded.

Data collection. Data abstracted included date of diagnosis of GCA, date of onset of LE claudication, and sex. Clinical symptoms of GCA, temporal artery biopsy (TAB) results, findings on peripheral vascular examination at onset of symptoms of LE claudication, and medications were recorded. Medical records were reviewed for presence of cardiovascular risk factors of hypertension, hyperlipidemia, diabetes, and smoking (never smoker, ex-smoker, or current smoker). These were said to be present if recorded by a physician, or if the patient was on therapy for one of these conditions. Laboratory information was abstracted for the following visits: baseline, first visit after institution of therapy for LE vasculitis, and at last followup. When available, findings from histopathology specimens from LE arteries were recorded. The imaging modality, distribution of arteries affected, type of vascular lesion, and followup imaging (if available) were documented. Outcomes measured included worsening or improvement of patient symptoms, addition of steroid-sparing therapy, surgical or percutaneous vascular intervention, and amputation.

Statistical analysis. The data were analyzed using descriptive methods with means, medians, and proportions.

RESULTS

We identified 6212 people evaluated for GCA at our institution between 1983 and 2007. Cross-referencing diagnostic codes for GCA/temporal arteritis with peripheral arterial disease/peripheral vascular disease/LE claudication/claudication/intermittent claudication, a medical index retrieval specialist identified 654 patients presenting between January 1, 1983, and June 30, 2007, for a diagnosis of GCA and peripheral arterial disease. We identified only 19 patients with GCA and documented LE vasculitis. Fourteen patients (73.7%) had histopathologic confirmation of GCA (12 on temporal artery biopsies, 1 on surgical pathology of a superficial femoral artery, and 1 patient with histologic evidence of GCA in both the temporal and superficial femoral arteries); 4 (21.1%) had imaging studies consistent with large-vessel vasculitis; and 1 (5.3%) had a clinical diagnosis of GCA based on symptoms and inflammatory markers.

Clinical features. The clinical characteristics of these 19 patients are summarized in Tables 1 and 2. All were women. Mean age at diagnosis of GCA was 70 years (standard deviation ± 7.99). Concurrent cranial symptoms (headache, jaw claudication, or vision changes) were absent in 42.1% of cases. All patients reported LE claudication. Sixteen patients (84.2%) had LE symptoms that preceded the diagnosis of GCA, by a median interval of 3 months (range 1–48); 11 of these had rapidly progressive LE claudication. Three patients (15.8%; Patients 1, 4, 11) developed LE claudication after a diagnosis of GCA; median time interval 16 months (range 9–34).

Seven patients (36.8%) had temporal artery abnormality on examination — 2 had swelling and 5 had diminished temporal artery pulses. All 19 patients had diminished pedal pulses. Abdominal or femoral bruits were auscultated in 9 cases (47.4%).

Erythrocyte sedimentation rate (ESR) was elevated (> 29 mm/h) in 16 patients. No information was available in 1 patient. Median ESR at diagnosis of LE vasculitis was 48 mm/h (range 13–103 mm/h). All 3 patients in whom ESR was normal had been started on prednisone (> 5 mg daily) by their local physician prior to evaluation at our institution.

TAB was positive in 13 of 15 patients (86.7%) in whom it was performed. One patient was diagnosed with GCA on surgical pathology of the superficial femoral artery obtained during endarterectomy (Figure 1).

Hypertension (47.4% of cases) was the most commonly noted cardiovascular risk factor, followed by hyperlipidemia (36.8%). Five patients (26.3%) had a history of smoking and 7 patients (36.8%) had no known cardiovascular risk factors. No patient had diabetes mellitus.

Imaging findings. All 19 patients had objective studies documenting peripheral arterial disease. GCA of the LE was diagnosed by conventional angiogram in 13 (68.4%), CTA in 2 (10.5%), and MRA in 1 (5.2%) (Figure 2). The superficial femoral arteries were most frequently involved, followed by the popliteal arteries. Fourteen patients (73.7%) had changes of vasculitis in more than 1 artery (excluding bilateral involvement). The most frequently observed finding was stenosis, followed by vessel occlusion. Aneurysmal changes were noted in 1 patient. Involvement was frequently bilateral. The distribution of vascular involvement is summarized in Table 3.

In 3 patients, only arterial Doppler studies were obtained which showed evidence of LE peripheral arterial disease. All 3 were included because of the temporal association of the onset of LE claudication with the diagnosis of GCA, lack of significant risk factors for peripheral arterial disease, and response to corticosteroid therapy. Subsequent arterial Doppler studies showed improvement in 2 of these patients after initiation of therapy (Patients 1 and 14).

Five patients (26.3%) had concurrent upper extremity involvement diagnosed by CTA in 2, conventional angiography in 1, and arterial Doppler studies in 2.

Therapy and outcomes. All patients were treated with glucocorticoids. Fifteen patients (79%) had improvement in their symptoms of claudication after institution of therapy. Five patients (26%) received further immunosuppressive therapy — 4 with azathioprine and 1 with oral cyclophosphamide followed by methotrexate.

Table 1. Clinical features of 19 patients with GCA and lower extremity (LE) vasculitis.

Patient	Sex	Age, yrs	New HA	Jaw Claudication	PMR	ESR	TAB	LE Study	CV Risk Factors	Treatment	LE Surgery
1	F	58	+	–	+	59*	+	Doppler	HTN	GC	–
2	F	58	–	–	–	35*	ND	Angio	None	GC	–
3	F	62	–	–	–	35	+	Angio	Lipid PS	GC, CYC, MTX	–
4	F	63	+	+	+	110	+	MRA	HTN, Lipid	GC, AZA	–
5	F	64	–	+	+	76	+	Angio	None	GC	–
6	F	66	–	–	–	80	ND	Angio	None	GC	+
7	F	66	+	+	+	40	+	Angio	HTN	GC	–
8	F	68	–	–	+	45	+	Angio	Lipid, PS	GC, AZA	+
9	F	69	–	+	+	NA	+	Angio	HTN, PS	GC	–
10	F	70	–	+	+	102	+	Angio	HTN, PS	GC, AZA	–
11	F	70	+	+	–	31	+	Angio	HTN, Lipid, PS	GC, AZA	+
12	F	71	+	+	+	35	+	Angio	None	GC	+
13	F	73	–	–	–	51	–	CTA	HTN, Lipid	GC	–
14	F	74	–	+	–	33	+	Doppler	None	GC	–
15	F	74	–	–	–	103	ND	CTA	HTN, Lipid	GC	+
16	F	76	+	+	–	57	+	Angio	None	GC	–
17	F	77	+	+	+	60*	–	Angio	None	GC	–
18	F	78	+	+	–	13*	ND	Doppler	HTN	GC	–
19	F	92	–	–	+	20*	+	Angio	Lipid	GC	+

* Patient was taking ≥ 5 mg prednisone. HA: headache; PMR: polymyalgia rheumatica; ESR: erythrocyte sedimentation rate; TAB: temporal artery biopsy; CV: cardiovascular; +: present; –: absent; NA: not available; ND: not done; angio: conventional angiogram; CTA: computed tomography angiography; MRA: magnetic resonance angiography; HTN: hypertension; PS: prior smoker; GC: glucocorticoid; AZA: azathioprine; MTX: methotrexate; CYC: cyclophosphamide.

Table 2. Clinical characteristics of 19 patients with giant cell arteritis (GCA) and lower extremity (LE) vasculitis.

Characteristic	No. Patients with GCA and LE Vasculitis
Female, n (%)	19 (100)
Mean age at diagnosis GCA, yrs (standard deviation)	70 (7.99)
LE symptom onset prior to diagnosis GCA, n (%)	16 (84.2)
LE symptom onset after diagnosis GCA, n (%)	3 (15.8)
Symptoms of GCA, n (%)	
New headache	8 (42.1)
Jaw claudication	11 (57.9)
Diplopia	0
Transient visual loss	2 (10.5)
Permanent visual loss	0
Presence of any cranial symptoms at onset LE claudication, n (%)	11 (57.9)
Symptoms of polymyalgia rheumatica, n (%)	10 (52.6)
GCA on pathology, n = 16 (%)	14/16* (87.5)
Median ESR at diagnosis LE vasculitis, mm/h (range)	42.5 (8–103)
Upper extremity arterial involvement, n (%)	5 (26.3)
Cardiovascular risk factors, n (%)	
Hypertension	9 (47.4)
Hyperlipidemia	7 (36.8)
Current smoking	0
Former smoker	5 (26.3)
Diabetes	0

* GCA diagnosed on pathology from superficial femoral artery in 1 patient.

Median length of followup was 41 months (range 11–180 mo). Four patients had revascularization surgery and 1 patient underwent percutaneous revascularization. In 3 cases, the revascularization procedure was performed prior to the diagnosis of GCA for presumed atherosclerotic disease (Patients 6, 8, 15). Three had ischemic ulcers (Patients 11, 12) and/or LE digital infarcts (Patients 12, 19) at diagnosis. Two of these (Patients 12, 19) underwent revascularization surgery despite treatment with high-dose prednisone, at 2 and 4 months after diagnosis, respectively. Pathology was available in 3 of 5 cases and showed changes of arteritis in 2 patients (Patients 6 and 12). Patient 6 had changes of arteritis with a focus of giant cells at the intimal-medial junction on pathology of the right superficial femoral artery (Figure 1), while surgical pathology from Patient 12 showed occlusive arteritis with chronic arteritis of all major arterial vessels. Despite revascularization, Patient 12 underwent a right above the knee amputation and Patient 19 underwent bilateral below the knee amputations for gangrene. Patient 11 required a toe amputation.

DISCUSSION

Extracranial vasculitis is a well recognized feature of GCA. LE vasculitis from GCA has been well documented on histopathology[4-9]. Despite this known complication, symptomatic LE vasculitis from GCA is rare[3]. However, it is important to distinguish this rare entity from atherosclerotic

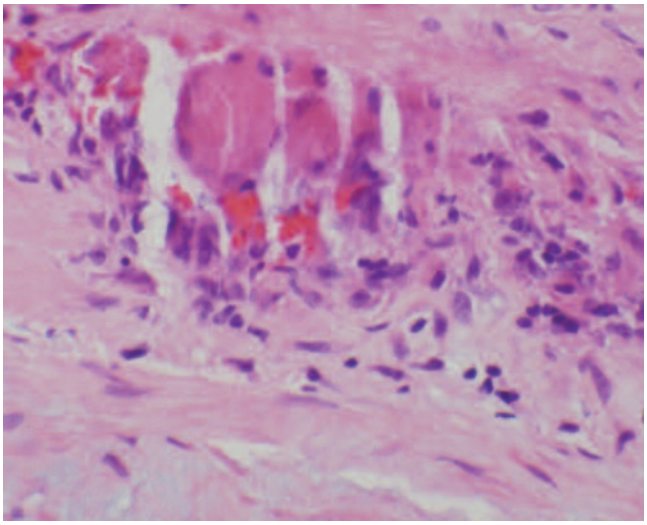

Figure 1. Pathologic specimen of the right superficial femoral artery from Patient 6 showing a focus of giant cells at the intimal-medial junction.

peripheral vascular disease since the treatment is very different. Our study describes the clinical findings and outcomes of 19 patients with LE vasculitis attributed to GCA evaluated at a tertiary care institution over a 25-year period. To our knowledge, this is the largest clinical case series of symptomatic LE vasculitis from GCA seen at a single institution.

From over 6000 patients evaluated at Mayo Clinic for GCA during the study period, we identified only 19 patients with GCA and confirmed LE vasculitis attributable to GCA. We used rigorous criteria for patient selection, including temporal association of LE symptoms with the diagnosis of GCA, presence of elevated inflammatory markers, and evidence of radiographic changes of vasculitis in most cases. These criteria, as well as the clinical response to therapy with glucocorticoids, all strongly suggest that the patients had LE vasculitis.

All 19 patients were women. Predominantly female sex was also noted in a previous clinical case series of 8 patients

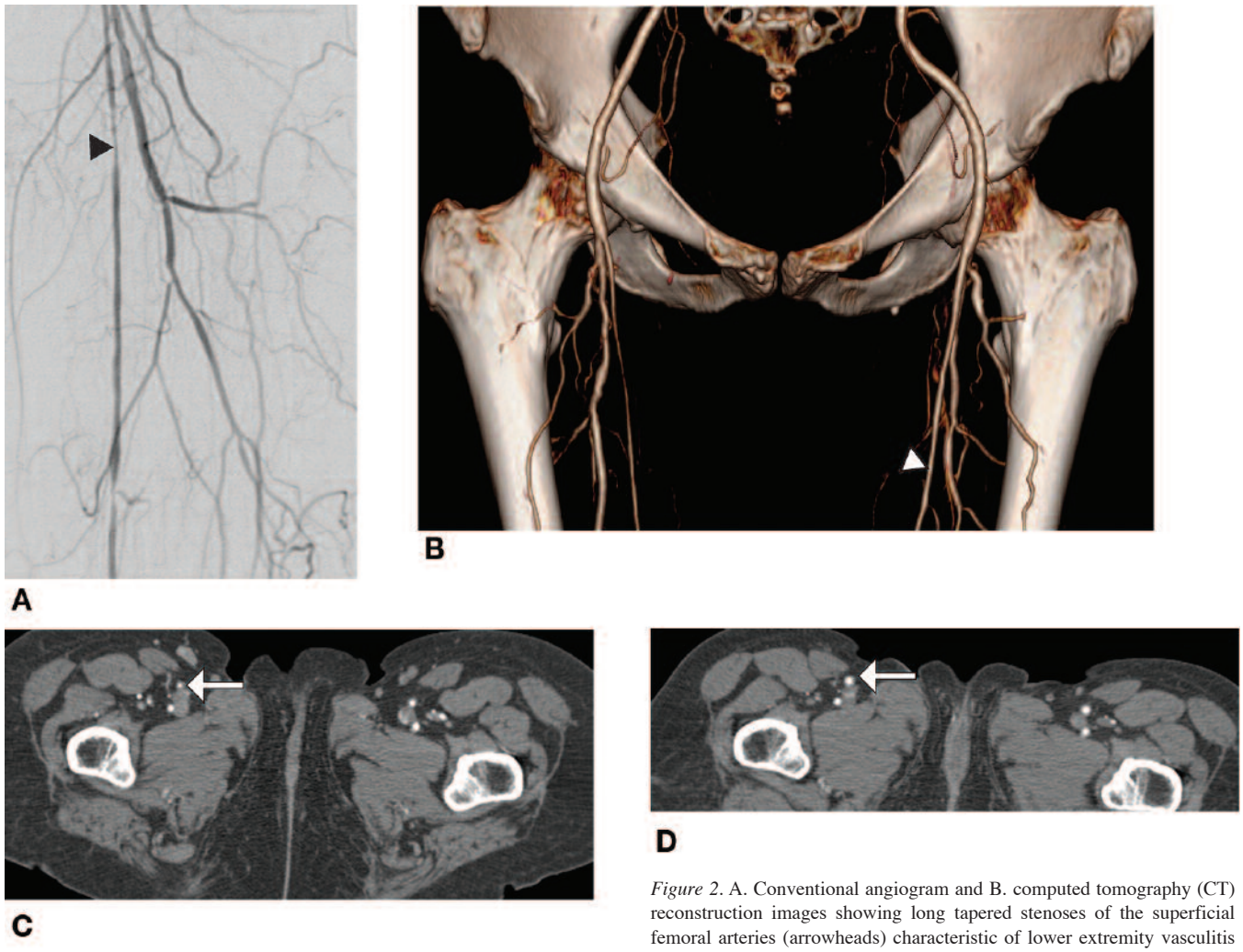

Figure 2. A. Conventional angiogram and B. computed tomography (CT) reconstruction images showing long tapered stenoses of the superficial femoral arteries (arrowheads) characteristic of lower extremity vasculitis from GCA. CT axial images show wall thickening of the superficial femoral artery (arrows) before therapy (C) and after therapy (D).

Table 3. Distribution of arterial involvement in 19 patients with giant cell arteritis and lower extremity vasculitis.

Artery Involved	Total no. of Patients	No. of Patients with Unilateral Involvement	No. of Patients with Bilateral Involvement
Common iliac artery	3	2	1
Internal iliac artery	2	0	2
Common femoral artery	4	2	2
Superficial femoral artery	13	1	12
Deep femoral artery	4	1	3
Popliteal artery	12	1	11
Infrapopliteal arteries	9	2	7

with LE vasculitis[4]. However, 2 of the patients in that series[4] were < 50 years old and therefore would not meet the usual age criterion for GCA according to the American College of Rheumatology classification[10]. The authors of this study[4] also reviewed 18 similar cases of LE vasculitis from GCA from the literature, of which 15 (83.3%) were women[4].

We are unable to comment on whether there is an association between sex and LE vasculitis in GCA without a control group. Aortic arch syndrome was associated with female sex in a case-control study comparing patients with upper extremity large-vessel occlusive disease from GCA to controls with cranial GCA[11]. Another possible explanation for the sex distribution noted in our series is that LE disease in men is likely to be attributed to atherosclerotic disease and therefore less severe cases of LE vasculitis from GCA may be underrecognized.

Only 3 patients in this series had an established diagnosis of GCA prior to developing LE symptoms. In 16 patients, LE claudication was the presenting symptom that led to the diagnosis of GCA. Eight of these 16 patients had no concurrent cranial symptoms (headache, vision loss, or jaw claudication) to suggest a diagnosis of GCA. This finding is similar to previous observations that cranial symptoms may be absent in a subset of patients with large-vessel GCA. In the earlier clinical series of 8 patients with LE vasculitis from GCA, cranial symptoms were present only in 50% of cases[4]. A review of 18 other published cases of LE vasculitis from GCA (histopathologically confirmed) yielded similar results, with headache in only 3 patients (16.7%)[4]. Cranial symptoms (headache, scalp tenderness, abnormal temporal arteries) were negatively associated with large-artery stenosis in a population-based study[3]. A study evaluating features that distinguish large-vessel GCA (subclavian, axillary, and proximal brachial vasculitis) from cranial GCA reported that only 11 of 74 patients (14.9%) with large-vessel GCA had symptoms of headache, jaw claudication, or visual symptoms at presentation[11]. TAB was negative in 42% of these patients with large-vessel GCA. Despite absence of any cranial symptoms, TAB was performed in 4 patients in our series for suspicion of large-vessel vasculitis from GCA and was positive in 3 cases.

Most patients in our series were diagnosed with LE vasculitis on conventional angiography. This is likely partly due to the indication, which was presumed atherosclerotic disease, and in part due to the time period over which the study was performed. Angiography showed a typical arteriographic pattern of vasculitis in most cases with bilateral smooth, long, tapered stenosis. This is similar to the findings described in previous studies[4,12,13]. In our series, disease was frequently bilateral and 14 patients had involvement of more than 1 artery (not including bilateral disease). The superficial femoral and popliteal arteries were the most commonly affected in our series. Only 5 patients had concurrent upper extremity involvement. However, not all patients were systematically screened.

A striking finding in our study was the paucity of significant conventional risk factors for peripheral arterial disease (PAD). Seven patients (36.8%) had no identifiable risk factors for PAD, while 4 patients had only 1 risk factor. In the series by Le Hello and colleagues, most patients also had only 1 identifiable risk factor for peripheral vascular disease[4]. Data from the National Health and Nutrition Examination Survey (NHANES) estimated the prevalence of PAD at 14.5% in people over the age of 70 years[14]. In this survey, 95% of people with prevalent PAD had at least 1 risk factor (hypertension, current smoking, diabetes, and hyperlipidemia). Current smoking, diabetes, and cardiovascular disease were the most highly associated with prevalent PAD[14]. Absence of risk factors for PAD should alert the physician to the possibility of an alternative diagnosis. In some cases it may be difficult to distinguish atherosclerotic disease from vasculitis. However, a careful medical history, measurement of biomarkers of inflammation, and appropriate imaging studies can be helpful in distinguishing atherosclerotic disease from vasculitis.

Finally, LE vasculitis was associated with significant morbidity. Five patients in our series underwent a revascularization procedure. In 3 cases (Patients 6, 8, and 15), intervention preceded the diagnosis of GCA and the procedure was performed for a presumed diagnosis of atherosclerotic disease. One of the patients (Patient 6) was found to have GCA on histopathologic examination of the superficial femoral artery for which prednisone was initiated postoperatively. The remaining 2 patients had persistence of symp-

toms despite intervention, and further evaluation led to the diagnosis of GCA. Their symptoms improved after therapy with prednisone. Two patients required revascularization surgery despite prednisone therapy. Both had ischemic ulcers and/or digital infarcts. Limb amputation was performed in both these patients for failed revascularization. Another patient underwent toe amputation. Luminal stenosis in GCA is caused by rapid, concentric intimal hyperplasia[15]. In some patients, the vascular response to injury characterized by intimal hyperplasia may progress despite corticosteroid therapy[15]. All patients in this series were treated with corticosteroids, with lessening of claudication symptoms in 15 patients, suggesting that the LE claudication was due to vasculitis rather than atherosclerotic disease.

Our study has several limitations. All patients in this series were evaluated at a tertiary care institution and therefore, the study is susceptible to referral bias. These patients may not represent patients seen in the general population, where atherosclerotic PAD remains the most common vascular cause of LE claudication. No sufficiently large population-based cohorts of patients with GCA exist to confidently establish the incidence or prevalence of this complication. The study was retrospective and therefore we were only able to abstract information already present in the medical record. Histologic documentation of LE vasculitis from GCA was available in only 2 cases in this series. In the remainder of the cases, we used typical features of vasculitis recorded on arterial imaging to establish the diagnosis of LE vasculitis.

The angiographic (conventional, CTA, or MRA) changes noted in all patients were consistent with those described for large-vessel vasculitis and most patients improved with glucocorticoid therapy. A limitation of conventional angiography, which was used to establish the diagnosis of LE vasculitis in most of our cases, is that while it provides information about the vessel lumen, it does not provide information about the vessel wall. Currently, CTA, MRA, and positron emission tomography (PET) scans have been increasingly used for evaluation of vasculitis[16]. CTA and MRA can show increased wall thickness in the affected vessels and may be useful in establishing the diagnosis.

We included only cases of symptomatic LE vasculitis. Increased use of these imaging modalities may reveal subclinical LE involvement from GCA to be more common than previously thought. This point is illustrated by findings from a study evaluating peripheral arteries in patients with GCA using color Doppler sonography, in which 3 of 33 patients (9%) had changes suggestive of vasculitis in LE arteries[17]. Another prospective study using fluorodeoxyglucose (FDG)-PET revealed FDG uptake in the femoral and iliac arteries in 13 of 35 (37%) patients at diagnosis of GCA[18]. Those investigators found that bilateral arteries almost always had the same intensity of FDG uptake, indicating that GCA appears to have symmetric involvement. Finally, our patients with LE vasculitis were not screened systematically for upper extremity involvement, and therefore our study may underestimate concurrent upper extremity disease in these patients.

While symptomatic LE vasculitis from GCA appears to be unusual, physicians need to be aware of it and the morbidity associated with it. The diagnosis should be suspected when patients present with a systemic inflammatory process and new-onset, rapidly progressive LE claudication, especially in the absence of significant conventional cardiovascular risk factors. A subset of patients may present with isolated LE claudication in the absence of typical cranial symptoms of GCA. TAB may be negative, but vascular imaging findings are often helpful in establishing the diagnosis. It is important to differentiate LE vasculitis due to GCA from atherosclerotic peripheral vascular disease, since medical therapy in the latter condition is limited to platelet inhibitors and exercise. Prompt initiation of glucocorticoid therapy is important in these patients. If recognized early, it may be possible to avoid ischemic complications of LE vasculitis by proper treatment of the underlying disease.

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