What to do when the Diagnosis of Giant Cell Arteritis and Takayasu's Arteritis Overlap

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KEY WORDS: giant cell arteritis (GCA), Takayasu's arteritis (TA), upper limb claudication, vasculitis, brachio-axillary arteries

IMAJ 2015; 17: 123–125

Giant cell arteritis (GCA) is the most common form of systemic necrotizing vasculitis in people aged 50 years and older and preferentially involves the extracranial branches of the carotid artery and temporal artery. Biopsy is considered the gold standard for establishing the diagnosis. However, GCA may involve the aorta and its major branches, most commonly the brachiocephalic and subclavian arteries, with symptoms including upper/lower limb claudication and other signs of limb ischemia in more than 10% of the cases. The prevalence of involvement on radiography is even higher. Involvement of these large vessels makes it difficult to distinguish GCA from Takayasu's arteritis (TA), the second most common necrotizing vasculitis, which also involves large and medium branches of the aorta but usually affects a younger population [1].

We report an unusual case of vasculitis, classified as both GCA and TA, based on American College of Rheumatology (ACR) 1990 classification criteria, and illustrate the complexity of diagnosis and treatment in such overlapping cases.

PATIENT DESCRIPTION

A 78 year old woman was referred to our hospital due to severe pain in her left hand which began 5 months before her presentation. The pain, distributed from her left wrist up to her left shoulder, was described as continuous, accompanied by tingling and pallor not related to exertion. There was a further history of 2 year unintentional weight loss, jaw claudication, paresthesia and myalgia, the latter attributed to statin therapy. The patient denied any history of headaches or visual impairment.

Physical examination on admission revealed a blood pressure difference between arms, 125/80 mmHg on the right and undetectable on the left, weakened brachial and radial pulse on the left, and a murmur heard over the axilla and brachial artery on the right; no murmurs were heard over the subclavian arteries. No signs of acral ischemia were noted. The neurological examination was non-contributory. The rest of the examination was unremarkable.

Laboratory investigations during hospitalization revealed an elevated sedimentation rate (ESR) of 54 mm/hour (0–29 mm/h); the complete blood count and other routine laboratory tests including chemistry, liver, renal and thyroid functions as well as lipid profile were all within normal limits. Serology including rheumatoid factor, antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-DNA antibodies, cryoglobulins, C3 and C4 levels, anti-Ro/La antibodies, anticardiolipin antibodies, and hepatitis serologies were all negative. Lupus anticoagulant, anticardiolipin immunoglobulins (Ig) M and G, and anti-β2-GPI-IgM values were within normal limits.

Computed tomography angiography (CTA) demonstrated arterial thickening, occlusion of the left axillary artery, stenosis of the right axillary artery and a narrowing of both brachial arteries, left more than right. An additional chest and abdominal CTA performed for further assessment demonstrated similar findings, without evidence of micro-aneurysms or occlusion of visceral or pulmonary arteries or other involvement of the abdominal aorta. Ophthalmologic examination revealed no signs of retinal vasculitis. Due to the patient's advanced age, high ESR and slightly reduced left temporal artery pulse on follow-up examination along with the typical angiographic findings, GCA was suspected; prednisone 60 mg/day was started promptly followed by a unilateral left temporal artery biopsy which showed no signs of inflammation. After 3 weeks of prednisone therapy the patient reported reduction in the severity of the pain in her left arm, which had by then disappeared completely during rest but was exacerbated only by exertion. Therapy with steroids and later with methotrexate and azothiaprine led to several side effects. With steroid therapy alone, which was tapered down, the patient showed clinical improvement as well as normalization of ESR. However, throughout the treatment the patient was non-compliant with her medications.

Follow-up CT angiograms demonstrated neither progression nor amelioration of the vasculitis. Considered an atypical case of GCA, the patient was conservatively treated with steroids and was followed in the outpatient clinic for 2 years. Medical therapy was challenging due to partial remission, drug-induced complications, and non-compliance throughout treatment. Irreversible damage was revealed in the left brachial and axillary arteries on the angiogram, and residual

Table 1. Reported cases of GCA/LVV presenting as upper limb claudication

Case	Diagnosis	Age/ gender	Symptoms	Involved arteries	Treatment	Outcome	Reference
1	GCA	78/ F	Persistent left arm pain	Bilateral, axillobrachial	High dose CS, then tapered off	Partial clinical improvement post-CS therapy	Katz-Agranov *IMAJ* (present case)
2	GCA	76/ M	Vertigo, left arm claudication	Bilateral external carotid, bilateral axillobrachial	High dose CS followed by methotrexate due to relapse and CS intolerance	Clinical improvement post-CS therapy, several relapses, later remission	Kolossváry . *Int Angiol* 2005; 24: 202
3	LVV	71/ F	Intermittent left arm claudication	Internal L. carotid, L. subclavian	Multiple surgical bypass surgeries and CS therapy	Clinical improvement, later a severe relapse involving subclavian-axillary necessitating additional surgical bypass. Then clinically stable	Lambert *Clin Rheumatol* 1996; 15: 174
4	LVV	65/ F	Weakness of both arms, worse on exertion	Bilateral axillary, L. vertebral	CS therapy along with pharmacological bilateral cervical sympathectomy	Significant clinical improvement following surgery. Relapsed and treated with high dose CS therapy, then clinically stable	Lambert
5	LVV	63/ F	Bilateral upper extremity claudication	L. subclavian, R. axillary	High dose CS therapy and R. carotid artery endarterectomy	Clinical improvement, low dose CS maintenance therapy	Lambert
6	GCA	62/ F	Vascular symptoms of upper limb and deterioration in general condition	Bilateral post-vertebral	High dose CS therapy	Asymptomatic on long-term follow-up, no angiographic improvement on follow-up	Ninet *Am J Med* 1990; 88: 13
7	GCA	65/ F	Vascular symptoms of upper limb	Bilateral axillary	High dose corticosteroid therapy	Partial clinical improvement, no angiographic improvement on follow-up. Remained dependent on low dose CS maintenance therapy	Ninet
8	GCA	67/ F	Vascular symptoms of upper limb and deterioration in general condition	L. brachial-axillary, bilateral humoral	High dose corticosteroid therapy and transitory anticoagulation therapy	Clinical improvement; asymptomatic with maintenance therapy; angiographic normalization of affected arteries	Ninet
9	GCA	73/ F	Vascular symptoms of upper limb and deterioration in general condition	Bilateral subclavian axillary (NS)	High dose CS therapy and transitory anticoagulation therapy	Clinical improvement, no angiographic improvement	Ninet
10	GCA	70/ F	Vascular symptoms of upper limb	L. subclavian, R. axillary	High dose CS therapy	Persistence of intermittent claudication requiring maintenance therapy then lost to follow-up	Ninet
11	GCA	71/ F	Weakness and pain in upper extremities, chronic headaches	R. subclavian, R. axillary	High dose CS therapy	Clinical improvement, restored peripheral pulses	Van Damme *Angiology* 1989; 40: 593
12	GCA	78/ F	Gangrene of L. thumb, weakness in both upper extremities, painful mastication	L. subclavian, L. axillary, R. subclavian, R. axillary	Bypass surgery, high dose CS therapy	Clinical improvement, restored peripheral pulses	Van Damme
13	GCA / LAI	67/ F	Occipital headaches, bilateral arm claudication	Bilateral axillary	High dose CS therapy	NS	Stanson *Am J Roentgenol* 1976; 127: 957
14	GCA / LAI	67/ F	Claudication of left arm in patient with polymyalgia rheumatica	Bilateral axillary	High dose CS therapy	Clinical improvement, restoration of R. arm pulses	Stanson
15	GCA / LAI	59/ F	Arm claudication	Bilateral subclavian, bilateral axillary, R. internal mammary	High dose CS therapy	NS	Stanson
16	GCA / LAI	71/ F	Isolated arm claudication	L. axillary, R. brachial	High dose CS therapy	NS	Stanson

GCA = giant cell arteritis, LVV = large vessel vasculitis, TA = temporal artery, LAI = large artery involvement, CS = corticosteroids, NS = not specified

pain and functional impairment in both arms were reported by the patient.

COMMENT

Due to the clinical presentation and findings, our patient qualified for both GCA and TA, according to the 1990 ACR clinical criteria, as she met three of the five criteria for GCA and three of six for TA.

Involvement of the aorta and its large vessels has long been considered an unusual manifestation of GCA and more characteristic of TA. Hence, the involvement of large vessels in GCA can cause overlap in the diagnostic criteria of GCA and TA, both of which have similar histological abnormalities and share pathogenic pathways. Nevertheless, distinguishing between these diseases is thought to be important for defining the appropriate treatment and surveillance because, unlike GCA, TA has a chronic course with relapses and remissions and is associated

with substantial morbidity and mortality ranging from 3% to 15% [2]. The diagnosis is often delayed and is usually established only when arterial stenoses or occlusions are present. Its course usually extends for many years with varying degrees of activity, and there may be ongoing inflammation even in the absence of symptoms. Only 20% of patients have a monophasic and self-limited disease. Therefore, long-term immunosuppressive therapy is considered necessary to avoid complications. According to various studies, vascular interventions are performed in more than 50% of cases [2]. Although the course of illness in large vessel GCA is usually benign and comparable to that of classic GCA, in some studies vascular intervention is undertaken [3,4].

In a recent study comparing angiographic findings of GCA and TA, lesions in both vasculitides were generally symmetrical in paired arteries and contiguous in the aorta with only a few differences in patterns of arterial involvement. Carotid and mesenteric arterial disease was seen more frequently in TA, axillary disease was more frequent in GCA, and a tendency towards asymmetric involvement of the subclavian artery was seen in TA with a high frequency of left subclavian artery involvement in contrast to symmetric subclavian with concomitant axillary involvement in GCA. Most arterial lesions were stenotic or occlusive and no significant differences were observed between TA and GCA regarding the type of arterial lesions [5].

We searched the literature for GCA/TA overlap cases and found only one case, in English, which raised the question of large vessel GCA versus TA. There are, however, anecdotal reports and case series of GCA variants/subtypes, such as atypical or "pulseless large vessel (LV-GCA), involving upper extremities" or "isolated form of GCA" [Table 1]. In many of these cases the presenting symptom was similar to that in our patient, namely upper extremity pain and/or claudication, while others presented with severe signs of limb ischemia, Raynaud's phenomenon or constitutional symptoms. Characteristic symptoms of GCA, such as headache or visual disturbances, were absent in many cases, as in ours. The arteries most commonly involved were the subclavian, axillary and brachial arteries, and there was a female predominance similar to that in TA. Similar to our patient, biopsy-negative cases were common. Most cases, however, had clinical and radiographic findings sufficient for diagnosis, and responded to steroid therapy.

Therefore, subtle differences in the distribution of the arterial disease between GCA and TA suggest that they may even exist on a continuum within the same disease in which disease expression may be influenced by age-related factors such as hormonal, immunologic and vascular factors.

Treatment is challenging in both GCA and TA. Currently, the best evidence-based treatments include high dose steroids. However, 40.8–48% of GCA patients and 46–84% of TA patients require additional immunosuppressive agents to achieve remission and as steroid-sparing agents. Many patients received biologic agents (mainly infliximab), followed by methotrexate, azathioprine, cyclophosphamide or cyclosporine, which are particularly effective in cases of GCA resistant to adjunctive therapy with methotrexate/azathioprine. Various medical regimens are sufficient for partial or complete remission [3] in GCA and TA. However, in resistant TA patients interventional methods such as balloon angioplasty (percutaneous transluminal coronary angioplasty) and/or surgery (bypass, embolectomy, etc.) may be beneficial. These same interventional methods may be considered in resistant cases of GCA involving large vessels [4]. The disadvantage of invasive therapy is re-occlusion or restenosis and peri-procedural complications [4].

Our case presents the difficulties in managing a case of GCA/TA overlap. We conclude that there may be need for a revision of the diagnostic criteria for these large vessel vasculitides in an era of advanced radiological technologies, and emphasize the need to screen for involvement of large vessels in cases of GCA. Acknowledging that GCA may overlap with TA could result in a more prompt diagnosis and accurate management where the use of interventional treatment should be further investigated. These issues should be taken into account when devising new classification criteria for large vessel vasculitides. Our unusual case of GCA emphasizes the difficulty in diagnosis, treatment and surveillance of large vessel vasculitis based on current diagnostic criteria.

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"A government big enough to give you everything you want is strong enough to take everything you have"

Thomas Jefferson (1743-1826), American Founding Father, the principal author of the Declaration of Independence, and the third President of the United States. He was a spokesman for democracy