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CASE REPORT

Large-vessel Giant Cell Arteritis: A Rare Cause of Acute Upper Limb Ischemia – Case Presentation and Review

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ABSTRACT

Introduction: Acute upper extremity ischemia is an uncommon vascular emergency due to a relatively rich collateral network and low workload of the upper limb. Its consequences depend on the site and etiology of the arterial occlusion. **Case presentation:** Aiming to emphasize the emerging role of Doppler ultrasound in the diagnosis of acute upper limb ischemia, we report the case of a 70-year-old female, with severe left arm resting pain and digital cyanosis. Due to the patient's age and the presence of cardiovascular risk factors, cardioembolic or thrombotic arterial occlusion would have been the most likely diagnosis in this case, but the color Doppler ultrasound revealed severe left axillary arterial stenosis with hypoechoic wall swelling, being highly suggestive for arteritis. Temporal artery biopsy was performed, which confirmed giant cell arteritis. An excellent clinical response was obtained after initiation of treatment with corticosteroids. **Conclusion:** In acute upper limb ischemia, color duplex ultrasound provides quick information about the etiology and localization of arterial lesions, offering characteristic findings in case of large-vessel giant cell arteritis. The routine use of this method in patients with clinical signs of upper limb ischemia and the fact that atypical localizations of giant cell arteritis may be present lead to fewer delayed or missed diagnoses.

Keywords: acute upper limb ischemia, giant cell arteritis

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INTRODUCTION

Acute limb ischemia is defined as an abrupt reduction in arterial perfusion, usually producing new or worsening symptoms and signs, and it may potentially threat the viability of the affected limb. Generally, initial presentation is up to 2 weeks following the acute event.[1] The sudden occlusion of the upper limb arteries can be produced by various pathologies. The main cause of acute upper limb ischemia is cardioembolic occlusion in patients with atrial fibrillation. Arterial thrombosis resulting from atherosclerotic plaque erosion or ulceration can also generate acute occlusion. Many other cardiac and non-cardiac disorders have been identified as possible causes of upper limb acute ischemia, including arterial thoracic outlet syndrome, traumatic or iatrogenic occlusion, arterial aneurysm, fibromuscular dysplasia, arteritis, thrombophilia, essential thrombocytosis.[2] From a clinical point of view, acute upper limb ischemia represents a vascular emergency, and its prompt diagnosis and adequate treatment is mandatory for the prevention of dramatic complications.

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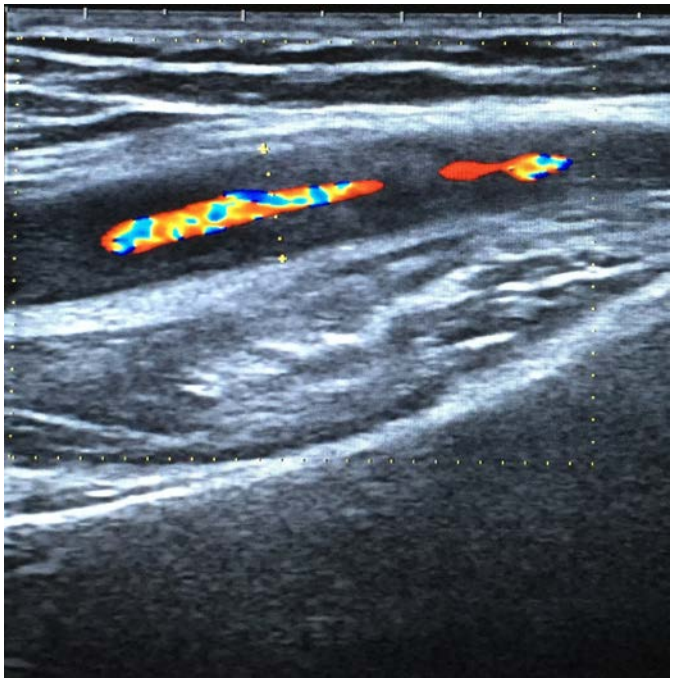

FIGURE 1. Left axillary artery ultrasound, longitudinal view, before treatment. Hypoechoic wall swelling (halo), size 1.8 mm.

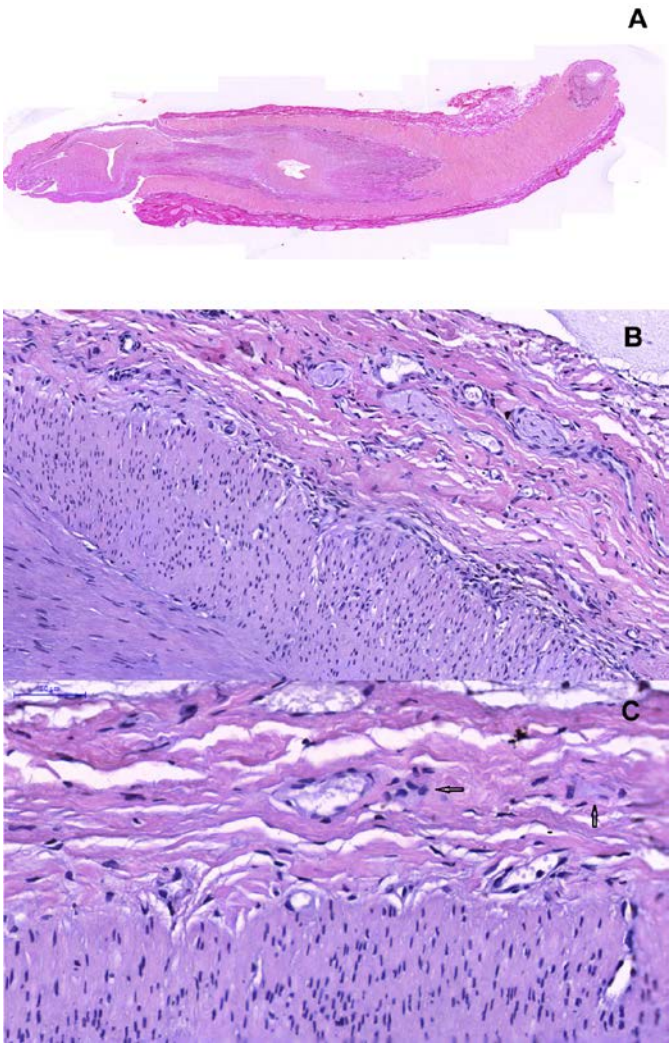

FIGURE 2. Narrowed vessel lumen with irregularly thickened intima and fibrotic media associated with disrupted elastic lamina (**A** – Elastic stain, 0.5 magnification). In the thickness of the wall there is a mild chronic inflammatory infiltrate (**B** – H&E stain, 4.5 magnification). The giant cells (arrows) and rare macrophages adjacent vasa vasorum are constant present (**C** – H&E stain, 10 magnification).

Giant cell arteritis (GCA) is the most frequent form of systemic medium- and large-vessel vasculitis with a predilection for the cranial branches of the carotid artery, typically affecting adults over 50 years of age. Clinically, it is characterized by a wide spectrum of symptoms secondary to the involvement of the cranial arteries: headaches, visual loss, stroke, jaw claudication. The prevalence of extracranial large vessel involvement (LV-GCA) was traditionally estimated at 3–15%, if only the cardinal GCA symptoms are considered. Autopsy studies on GCA patients have demonstrated histological signs of large-vessel involvement in 80% of patients, and imaging studies revealed extensive radiographic involvement of the aorta and its major branches in up to 83% of patients.[3,4]

CASE PRESENTATION

A 70-year-old Caucasian overweight woman, with known arterial hypertension, presented with severe rest pain in the left arm, coldness, pallor, and paresthesia of the left hand, and digital cyanosis. She had no other symptoms (e.g., headache, jaw claudication, malaise, fever, or visual disturbances). The patient described worsening left shoulder pain for several months, which had been interpreted as shoulder osteoarthritis by her general practitioner (GP) and was treated with non-steroid anti-inflammatory drugs without results. Clinically, she had cold and cyanotic hands with impalpable radial and cubital pulses, and no measurable blood pressure on the left arm. Continuous wave (CW) Doppler examination revealed 140 mmHg systolic pressure on the right ulnar and radial arteries, and 30 mmHg on the left ulnar and radial arteries.

Due to the patient's age and the presence of cardiovascular risk factors, atherosclerotic upper limb arterial disease would have been the most likely diagnosis in this case. The color duplex sonography (CDS) examination revealed a hypoechoic concentric rim of wall swelling (halo) around the lumen of the left axillary artery (AXA), with turbulent flow and localized increased flow velocity (210 cm/s) (Figure 1). In longitudinal view, the halo size was 1.8 mm.

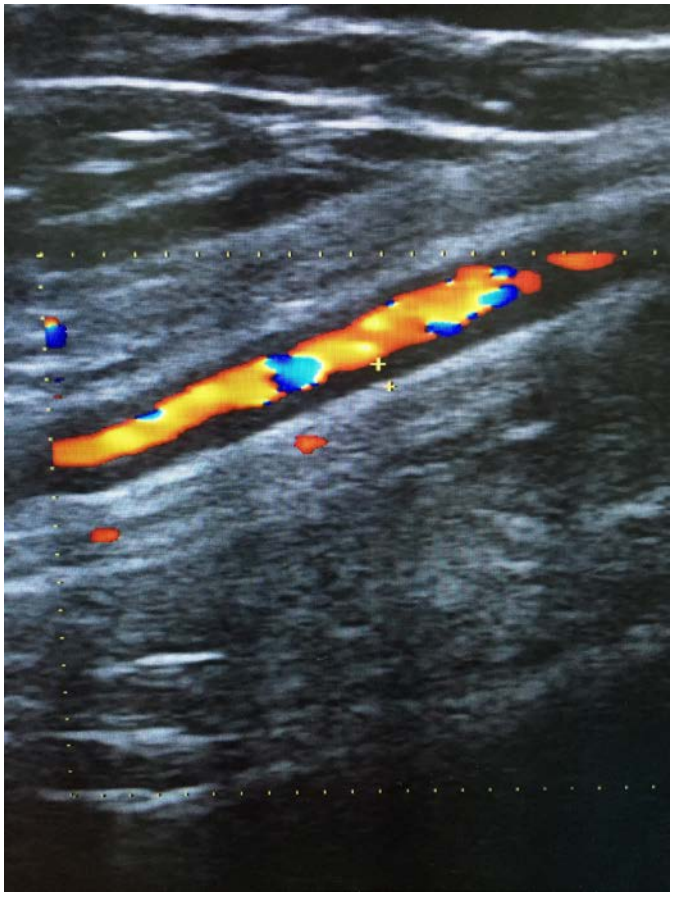

FIGURE 3. Left axillary artery ultrasound, longitudinal view, at 10 weeks of treatment. Hypoechoic wall swelling (halo), size 1.1 mm.

On the contralateral axillary, subclavian, carotid, and femoral arteries, only minimal atherosclerotic wall alterations were detected.

At the level of the temporal arteries (TA), clinically, no tenderness or constitutional symptoms were observed. The CDS of the temporal arteries revealed absence of flow and hypoechoic material in the right common superficial TA, and the presence of a homogenous, hypoechoic circumferential wall thickening (halo size 0.8 mm) in the left TA. The arteriography described smooth, concentric wall thickening of the left AXA with severe stenosis; no involvement of the subclavian artery, carotid artery, or the ascending aorta was detected.

The erythrocyte sedimentation rate was 121 mm/h; she had normochromic anemia, positive C-reactive protein (CRP), and a negative infectious and autoimmune workup. Chest radiograph was normal, with no evidence of cervical ribs or chronic aortic dissection. The 12-lead ECG revealed normal sinus rhythm.

TA biopsy was performed, which revealed a narrowed vessel lumen with irregularly thickened intima, a fibrotic media associated with disrupted elastic lamina, mild chronic inflammatory infiltrate, and giant cells confirming GCA (Figure 2).

On the basis of the CDS finding, positive TA biopsy, and arteriography results, as well as on the systemic inflammatory response, extracranial GCA was diagnosed. High-dose glucocorticoid therapy (0.75 mg/kg per day prednisolone) was started. The patient was also started on clopidogrel (75 mg OD), due to increased risk of cardiovascular events, and proton pump inhibitors (pantoprazole 40 mg OD). The evolution was clinically favorable; the erythrocyte sedimentation rate was 43 mm/h at 2 weeks and 10 mm/h at 10 weeks after initiation of treatment. The follow-up CDS performed at 16 weeks revealed reduced swelling in the AXA wall (the halo size was 1.1 mm) (Figure 3).

DISCUSSIONS

Recognizing giant-cell arteritis as the cause of unilateral acute upper limb ischemia may be challenging, especially when typical symptoms of GCA (headache, fever, visual loss, polymyalgia rheumatica) are missing. Large-vessel involvement in patients diagnosed with GCA has been found in more than 80% of patients, as shown via imaging studies. The thoracic aorta (45–65%) and the subclavian arteries/AXAs (30–75%) are the most affected locations in case of LV-GCA. Positron emission tomography (PET) studies have shown that inflammation of the subclavian and axillary arteries is virtually always accompanied by thoracic aortitis. The involvement of large vessels is paramount because these patients present a high risk of developing thoracic aortic aneurysms, which in turn lead to increased mortality rates.[3,4]

CLINICAL AND LABORATORY FEATURES

GCA may present variable clinical signs depending on the affected arterial segment. In case of cranial GCA, classical signs and symptoms include headache, temporary artery tenderness and swelling, jaw claudication, visual disturbances.[3] These classical signs are generally absent in patients with LV-GCA. In these patients, limb claudication, pulse disturbances, vascular bruits, and aortic regurgitation murmur may appear. In addition, studies describe a younger age of disease onset, stronger female predominance, and longer time to diagnosis in case of patients with LV-GCA. Other common signs and symptoms of GCA and LV-GCA include fever of unknown origin, weight loss, malaise, elevated erythrocyte sedimentation rate, normochromic anemia, positive CRP, and a negative infectious and autoimmune workup. In some cases, overlapping phe-

TABLE 1. Clinical signs and symptoms of LV-GCA and GCA[4,18–20]

Sign and symptoms	LV-GCA	GCA
Headache	+/–	++
Visual symptoms	–	++
Temporal artery tenderness/swelling	+/–	++
Fever	+	+
Weight loss	+/–	+/–
Jaw claudication	–	+
Tongue pain	–	+
Limb claudication	++	–
Blood pressure difference	++	–
Vascular bruits	+	–
Elevated ESR	++	++
Elevated CRP	+	+

TABLE 2. Ultrasonographic findings in LV-GCA[8–10]

Ultrasonographic sign	Description
Halo sign	Hypoechoic, homogenous wall swelling, commonly concentric, visible both in longitudinal and transverse scans
Maximum halo size	Measured in longitudinal view in mm Cut-off values: 1.5–2 mm in the AXA, 0.5–0.8 mm in the TA
Compression sign	The halo does not disappear after applying pressure with the transducer, even if the vessel lumen remains occluded (in TAs)
Stenosis	Segmental increased flow velocity (more than twice before or behind the stenosis), flow turbulence (mosaic), reduced post-stenotic velocity and reduced velocity behind the area of stenosis
Occlusion	Hypoechoic material in the vessel lumen, absence of flow after the occlusion

notypes may be observed.[4] The characteristic clinical signs and symptoms of LV-GCA and GCA are presented in Table 1.

Vasculitis should always be part of the differential diagnosis in large artery obstruction, even in patients with multiple cardiovascular risk factors. Vascular inflammation must be differentiated from atherosclerotic changes in patients over 50 years. The two disorders present different locations (atherosclerosis is more common in the iliac, femoral, common and internal carotid arteries) and morphology of lesions.[4] As stated in the 2017 ESC Guidelines, in case of upper limb ischemia, the differential diagnosis should include atherosclerosis, thoracic outlet syndrome, arteritis, radiation artery fibrosis, embolic origin, and fibromuscular dysplasia.[1]

THE ROLE OF COLOR DUPLEX SONOGRAPHY IN THE DIAGNOSIS OF LV-GCA

The development of noninvasive imaging methods (CDS, magnetic resonance angiography, computed tomography angiography, PET) has significantly improved the diagnosis of LV-GCA. However, a consensus statement on the diagnostic criteria of large-vessel involvement as well as the modality and timing of evaluation is lacking.

A case-control study that included subjects with new-onset GCA has identified large-vessel involvement in 29% of cases, by using CDS.[5] Large-vessel involvement was also noted in 30% of 176 patients with GCA, with the use of CDS for imaging evaluation of the subclavian, axillary, proximal brachial, and temporal arteries.[6]

Color duplex sonography is the most accessible diagnostic tool for the rapid diagnosis of LV-GCA, this method being supported by increasing robust evidence.[7–9] The benefits of CDS include its wide accessibility, the absence of ionization radiations, and low costs. However, the method is characterized by relatively high inter-reader variability; therefore, the evaluation of large vessels should be performed by experienced ultrasonographers. The halo sign is the most important and typical ultrasonographic finding in vasculitis, being a hypoechoic homogeneous area easily identifiable between the vessel lumen and the perivascular tissue.[7,8] In GCA, edema and cell infiltrates are located in the media and extend to the intima; the ultrasound detects this edematous parietal change as a hypoechoic material around the artery lumen that contrasts to the surrounding tissues. It can be circumferential or eccentric in axial views and may be confirmed by a positive "compression sign" in the temporal arteries and its branches, meaning that the halo does not disappear after applying pressure with the transducer, even if the vessel lumen remains occluded.[8,9] The most important ultrasonographic findings in LV-GCA are presented in Table 2.

A recent prospective study published by Schaffer *et al.* has established that normal intima-media thickness (IMT) is approximately 0.2 mm in the TA and 0.6 mm in the AXA. Vasculitis changes commonly result in 0.5–0.8 mm wall swelling in TAs and 1.5–2 mm in AXAs.[10]

Czihal *et al.* aimed to determine the diagnostic accuracy of CDS of the TAs and AXAs for the diagnosis of GCA. Their results revealed that for the diagnosis of LV-GCA, a cut-off value of ≥1.2 mm in intima media thickness evaluated in the AXA offers a sensitivity and specificity of 81.3% and 96.1%, respectively.[11]

The presence of a halo on CDS is considered a sign of disease activity. In the TAs, this hypoechoic wall swelling may resolve within a few days after glucocorticoid treatment initiation, but AXAs may take 1–2 months.[8] Long-term monitoring of disease activity is important in patients with LV-GCA given the risk for vascular complications. However, consensus guideline recommendations on the method, duration, and timing of follow-up of these patients are lacking.[4]

THE ROLE OF OTHER IMAGING TECHNIQUES IN THE DIAGNOSIS OF LV-GCA

Medical and vascular surgical guidelines recommend baseline computed tomography angiography (CTA) or magnetic resonance angiography (MRA) evaluation in all patients with GCA or LV-GCA in order to evaluate the presence and extension of aortic involvement.[12] A prospective study conducted by Prieto-Gonzalez *et al.* has evaluated the presence of large-vessel involvement in newly diagnosed GCA, as assessed by CTA, and has detected signs of large-vessel vasculitis in 67.7% of cases. The involved vessels were as follows: aorta (65%), brachiocephalic trunk (47.5%), carotid arteries (35%), subclavian arteries (42.5%), AXAs (17.5%).[13] Several retrospective and cross-sectional imaging studies have shown the presence of structural damage in the aortic wall in 10–33% of patients with GCA in a follow-up period of 10 years.[14,15] The 18F-fluorodeoxyglucose (18FDG)-PET evaluation of GCA patients has demonstrated vascular hypermetabolism as a sign of vascular inflammation in large elastic arteries in up to 85% of cases.[16] This method can detect early therapeutic response in patients with GCA, being a useful tool for assessment of disease activity.[8]

THERAPEUTIC APPROACH OF PATIENTS WITH LV-GCA

Studies comparing glucocorticoid effects and doses or immunosuppressive therapeutic regimens, especially for LV-GCA, are missing. Generally, subjects with signs of LV-GCA should be prescribed the same treatment regimen as patients with cranial GCA. The goal of treatment in patients with LV-GCA is rapid disease control by suppressing systemic and vascular inflammation, thus preventing ischemic organ damage.

Glucocorticoids (GC) are the treatment of choice for inducing remission in subjects with LV-GCA. Initial doses of 0.75–1.0 mg/kg/day, followed by gradual tapering is the regimen of choice.[4] A prospective study evaluating the early outcomes of standardized GC treatment in biopsy- and CTA-proven LV-GCA has revealed a decrease in inflammation at the level of the large vessels after a follow-up time of 13.5 months (decreased number of affected segments and decreased wall thickness).[17] The symptoms of GCA generally respond quickly to high-dose GCs with rapid reduction of inflammatory markers. GC dose-reduction should be considered in the absence of clinical symptoms and laboratory abnormalities (erythrocyte sedimentation rate, CRP). Patients should be monitored for evidence of relapse, in which case adjuvant therapy, such as methotrexate or other immunosuppressant, must be considered.[18–20]

CONCLUSIONS

Large-vessel involvement in GCA is a frequent disorder, and a multidisciplinary approach with a standardized CDS assessment of different vascular territories is needed to prevent the delay in diagnosis and consequent vascular complications. CDS is the most accessible tool for the rapid diagnosis of LV-GCA, this method being supported by increasing robust evidence. The routine use of this method in patients with clinical signs of upper limb ischemia and the fact that atypical localizations of disease are common lead to fewer delayed or missed diagnoses.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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