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Early large vessel systemic vasculitis in adults

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A B S T R A C T

Giant cell arteritis (GCA) is the most common vasculitis in individuals older than 50 years in Western countries. In addition to the typical pattern of cranial ischemic manifestations, large vessel vasculitis (LVV) involvement has emerged as a common feature of GCA. Patients with predominant LVV manifestations differ from those with the cranial pattern. They are usually affected at a younger age and often have nonspecific manifestations such as constitutional syndrome, fever of unknown origin, or refractory/atypical polymyalgia rheumatica (PMR). In these patients, cranial manifestations are often absent. Furthermore, patients with isolated PMR should be followed up because of the potential risk of severe vascular complications in the setting of an underlying GCA. Whereas temporal artery biopsy and/or color duplex ultrasound of the temporal arteries is useful for the diagnosis of cranial GCA, Doppler sonography of the subclavian and axillary arteries, fluorine-18-fluorodeoxyglucose–positron emission tomography/computed tomography, magnetic resonance, and computed

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tomography-angiography are very useful to identify the presence of LVV, and they may play a potential role in the follow-up of these patients.

Introduction

The 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides defines large vessel vasculitis (LVV) as a condition that affects large arteries more often than other vasculitides [1]. Takayasu arteritis (TKA) and giant cell arteritis (GCA) are the 2 main types of LVV. They share histopathologic features and are more common in women [1]. However, TKA occurs mainly in young individuals, whereas GCA is a vasculitis predominantly involving elderly people [1].

GCA affects the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries, in individuals 50 years and older with a peak of incidence in the 70–80 age group [2]. There is a North–South gradient in the incidence of GCA in Europe, being more common in Norway, Sweden, or Denmark than in Italy or Spain [3]. GCA is more common in individuals of Scandinavian background [3]. The genetic influence of GCA has been confirmed by a number of studies that supported a strong association of this vasculitis with the HLA class II region, in particular with HLA-DRB1*0401 [4,5*].

In this article, we have discussed different aspects of GCA, the prototype of LVV in adults, focusing on the clues that may be useful to make an early diagnosis of this vasculitis.

LVV in adults: GCA is not only a cranial disease

For years, GCA was considered a typical cranial vasculitis involving predominantly the temporal artery and the extracranial branches of the carotid artery as well as arteries derived of the ophthalmic artery that, in turn, is a branch of the internal carotid artery. This is the reason why GCA was also called “temporal” arteritis. Headache is a typical symptom in patients with this predominant pattern, which may alert the clinician about the presence of GCA. Other features include scalp tenderness; a nodular, tender, and thickened temporal artery; or jaw claudication. Polymyalgia rheumatica (PMR) features are often present, and they may constitute the presenting manifestation of GCA [6]. Other features such as facial pain or dysphagia are often reported by these patients.

Early diagnosis of patients with the classic cranial pattern of GCA is very important due to the high risk of visual ischemic complications and, less commonly, of cerebrovascular accidents, mainly involving the vertebra-basilar territory, which occur soon after the onset of GCA symptoms [7,8].

Although GCA may be observed at any age in individuals older than 50 years, patients presenting with the typical cranial manifestations are generally older than 60 years, with the highest peak of incidence in the 70-80 decade of life [2]. Most of them exhibit significant elevation of acute phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive [CRP]) [6].

The diagnosis of GCA in patients presenting with the typical cranial pattern of this vasculitis is relatively straightforward. The presence of headache, in particular new-onset headache, occurring in a person older than 50 years, who does not have a past history of frequent headaches, should be considered as a “red flag” to suspect GCA. The probability of GCA would be higher if other cranial features or PMR is present. In this case, the assessment of routine laboratory parameters of inflammation, measuring ESR and CRP values, should be performed without delay. It is known that some patients with typical GCA may have low levels of acute phase reactants [9]. Nonetheless, the ESR and CRP are generally elevated in most patients with cranial GCA [10].

Although glucocorticoid therapy should not be delayed in an attempt to prevent the risk of permanent visual loss, diagnostic tests are useful to confirm a diagnosis of GCA. Among them, a temporal artery biopsy (TAB) was classically considered the gold test to make a diagnosis of patients presenting with typical cranial manifestations of GCA [11]. For this purpose, the length of TAB should be of at least 0.5 cm to avoid false-negative results [12], as the inflammatory infiltrate involving the temporal artery

is usually patchy, with areas showing disruption of the internal elastic lamina along with an inflammatory infiltrate composed of mononuclear cells with or without multinucleated giant cells alternating with areas without inflammation [11,12].

Noninvasive techniques such as the temporal artery ultrasound allow to identify patients with GCA along with cranial features [13]. In fact, several studies have demonstrated that ultrasonography (US) of the temporal artery may be an alternative to the TAB to make a diagnosis of GCA, in particular, in patients presenting with the typical cranial pattern of the disease. The assessment of the temporal arteries by Doppler US in these patients shows the typical feature, characterized by a dark, hypoechoic, circumferential wall thickening "halo" around the lumen of the temporal artery due to an edema of the artery wall [13,14,15*]. Of note, in patients with GCA, the "halo sign" persists despite firm compression on the artery applied with the US transducer (positive compression sign) [16*]. Other US findings that can be found in patients with cranial involvement of the temporal artery are the presence of stenosis and occlusion [14]. In contrast, the absence of this "halo sign" involving the temporal artery makes the diagnosis of cranial GCA unlikely [17]. As color duplex US is a noninvasive, reproducible, and inexpensive method with high sensitivity and specificity for the diagnosis of GCA in patients presenting with arteritic involvement of the temporal arteries, experts consider that the presence of positive US findings in the temporal artery would be unnecessary to perform a TAB. With regard to this, one of the EULAR recommendations for the use of imaging in LVV in clinical practice indicates that in patients in whom there is a high clinical suspicion of GCA, a positive imaging test allows to make the diagnosis of GCA without an additional test such as the TAB [18*]. Nevertheless, we advise that a TAB should always be done in all patients with cranial features. We observed that the presence of abnormalities of temporal arteries on the physical examination was associated with high predictive value for a positive TAB [19]. At this point, an issue of potential interest may be to determine whether a color duplex US-guided TAB performed at the site of the halo could prevent false-negative histological results and, therefore, be useful for the diagnosis of GCA. With regard to this, a study revealed that color duplex US-guided TAB did not yield a higher frequency of patients with positive TAB [20*].

As discussed before, prompt treatment has to be initiated in patients with suspected GCA, as the prognosis of visual complications is poor once that visual loss is established, and the probability of visual recovery is low unless medical treatment can be initiated within the first few hours after the development of the visual loss [21,22*].

Fig. 1 shows the workup of management in a patient presenting with the typical cranial pattern of GCA.

Early diagnosis of GCA in patients without a predominant cranial pattern of the disease is often more difficult. However, the advent of new imaging techniques such as magnetic resonance (MR)-angiography or computed tomography (CT)-angiography has redefined the actual spectrum of vascular involvement in patients with GCA [23]. It is also true for fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) [24*]. With regard to this, ^{18}F-FDG PET/CT has shown good performance both for the early diagnosis of LVV, even before the development of edema and structural changes of the vessel wall as shown by MR angiography, and for the evaluation of the extent of the disease [25,26].

Several studies have shown that Doppler US of the axillary and subclavian arteries are very useful to make a diagnosis of LVV in patients without cranial involvement. However, this technique has still a very variable profitability depending much on the operator experience [16*,27*,28*].

Patients with GCA and LVV involvement may have stenosis of the primary and secondary branches of the aorta. They often do not complain of the typical cranial ischemic manifestations. Clinicians should be aware of the potential risk of clinical signs of occlusive manifestations in GCA, mainly claudication of the upper extremities, due to subclavian, axillary, or brachial artery stenosis or, less commonly, of arteries or the lower extremities, which yield clinical signs of occlusive manifestations such as claudication of the extremities and tissue gangrene [29]. In others, however, the LVV involvement is overshadowed by the cranial ischemic manifestations. With regard to this, classic studies already emphasized that LVV involvement was not uncommon in the follow-up of patients with GCA. Unlike the abdominal aortic aneurysmal disease observed in patients with atherosclerosis, aortic aneurysmal disease involving more commonly the thoracic aorta can be seen in extended follow-up of some patients with GCA [29,30]. The knowledge of this complication is important, as thoracic aortic dissection is associated with increased mortality in these patients [31].

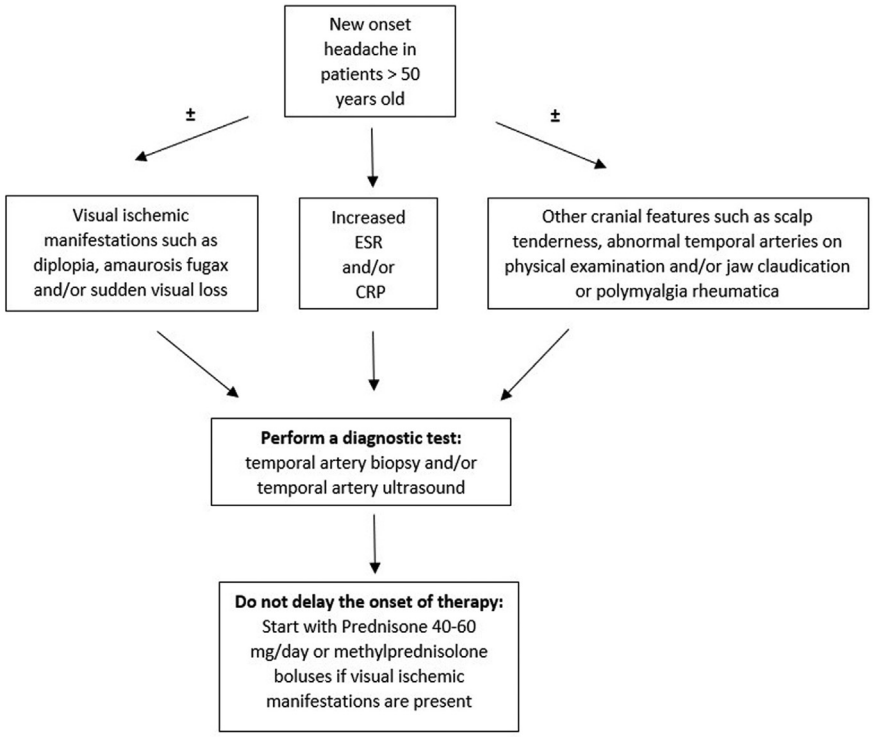

Fig. 1. Workup to suspect early GCA in patients presenting with the typical cranial pattern of GCA.

In a recent prospective, longitudinal, multicenter study that included 187 patients with cranial or LVV manifestations of GCA, 66% of patients had at least one arterial lesion on first imaging study. The most frequently observed vascular lesions in decreasing frequency were observed in the subclavian (42%), axillary (32%), and thoracic aortic (20%) [32*]. New vascular lesions on serial imaging during the follow-up were more commonly observed in those patients with diagnosis of GCA based on LV imaging [32*]. These findings support the use of imaging techniques to identify the presence of LVV, both at the diagnosis and during the follow-up of patients with GCA. With regard to this, the use of the imaging techniques has allowed to identify more patients with GCA along with the predominant LVV pattern of the disease. These patients tend to be affected at a younger age than those with the classic cranial manifestations, often below 65–70 years old, and they usually have a mild or moderate elevation of ESR ad CRP. In these patients, cranial manifestations may be absent or they do not represent the main complaint of the patient.

Classic studies described biopsy-proven GCA patients without cranial ischemic manifestations, with unexplained anemia, fever of unknown origin, constitutional symptoms, or a refractory PMR [33,34]. Imaging techniques have shown that these patients have a predominant LVV.

GCA may be a diagnosis of exclusion in patients assessed for the presence of an infection or malignancy. At this point, MR-angiography or ^{18}F-FDG-PET/CT scan has turned out to be very useful for the diagnosis of these patients, as the TAB yield is lower than the observed value in patients with predominant cranial ischemic manifestations [35].

Table 1 illustrates imaging features that may be observed in patients with GCA with LVV involvement [23,36,37*].

Fig. 2 shows the workup suggested for an early diagnosis of patients with GCA along with predominant LVV involvement. Although symptoms in patients with predominant LLV are often nonspecific, vascular abnormalities such as bruits (vascular murmurs) and asymmetric or absent pulses may be a clue for the diagnosis of LVV. These patients may also present pain and or arm claudication or

Table 1
Imaging features that may alert during LVV involvement in GCA.

Imaging technique	Main findings
MR-angiography	Uptake of contrast media (e.g., gadolinium) in the aorta Contrast enhancement and wall edema Aortic circumferential wall thickening Vascular stenosis and/or vascular dilatation and aneurysms
CT-angiography	Contrast enhancement Aortic circumferential wall thickening Vascular stenosis and/or vascular dilatation and aneurysms
^{18}F-FDG-PET7CT-scan	Increased FDG uptake: Augmented homogeneous metabolism
Color Doppler US	Typically, the axillary arteries and, less commonly, the subclavian and/or proximal brachial arteries show vasculitis wall swelling manifested as a marked, hypoechoic circumferential wall thickening

Computed tomography (CT).
Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT).
Large vessel vasculitis (LVV).
Magnetic Resonance (MR).

pain on mild exertion such as walking, predominantly in the calves and legs, which improves by a short period of rest. These features clearly alert during the presence of LVV.

Fig. 3 shows a 59-year-old woman with unremarkable past history, who was initially diagnosed as having isolated PMR in another center. She denied headache or any other cranial features of GCA. However, when prednisone dose was tapered, she started to complain of claudication in the legs while walking, which subsided with rest. On physical examination, the dorsalis pedis, the posterior tibial, and the popliteal pulses were absent in her right leg, and they were weak in the contralateral left leg. The ESR was 55 mm/1st hour and the CRP 69.15 mg/L ^{18}F-FDG PET/CT scan disclosed signs of bursitis in the setting of PMR along with intense FDG uptake in the blood vessels including the femoral arteries. A lower

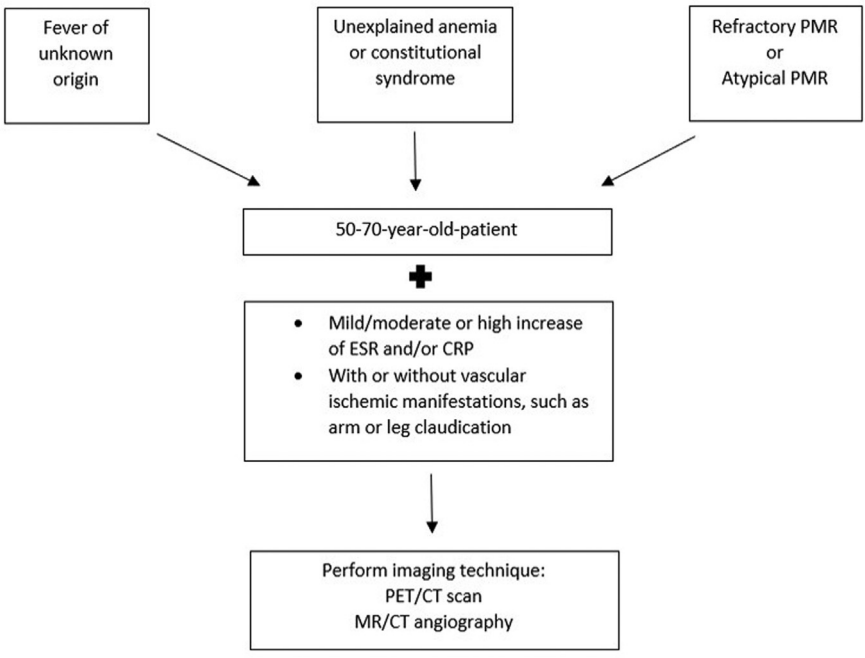

Fig. 2. Workup for early diagnosis in patients with predominant extracranial LVV features of GCA.

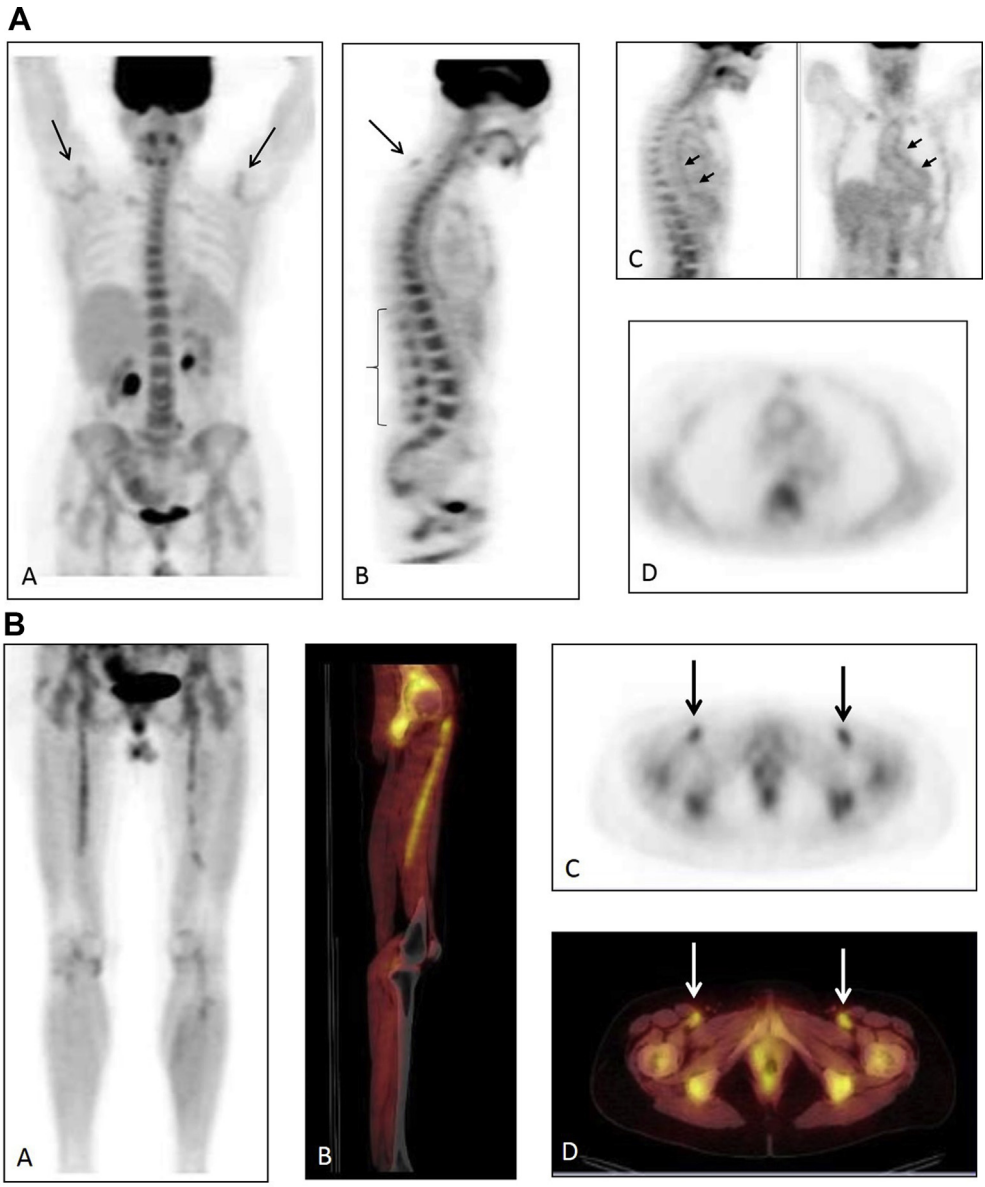

Fig. 3. A: A–D: ^{18}F-FDG PET/CT scan showed increased metabolism involving the sternoclavicular joints, shoulders, and cervical and dorsolumbar interspinous bursae (long arrows). These scintigraphy findings were in accordance with the suspected PMR. 3C, shows moderately increased uptake of ^{18}F-FDG in the thoracic aortic wall (short arrows). B: A–D: ^{18}F-FDG PET/CT scan also showed intense uptake along the femoral arteries (arrows) from the inguinal region to the lower third of the thighs and a less intense uptake in the thoracic aorta wall (as can be seen in Fig. 3A), suggesting LVV.

extremity arteriography showed obstruction of femoral arteries. In this patient, a TAB yielded negative results. This case highlights the importance of the clinical examination in patients with suspected GCA. It should include the palpation of the pedal pulses. If these pulses are not palpable and particularly if patients complain of lower limb claudication and there is no history of conditions or traditional cardiovascular risk factors associated with atherosclerotic disease, a diagnosis of LVV has to be considered.

With regard to the follow-up of patients with LVV, recent data support the use of ^{18}F-FDG PET/CT for the management of these patients. This imaging technique provides a single examination of the whole body, not only an early diagnosis of LVV and a precise evaluation of the extent of the disease in comparison to the structural imaging techniques but also a more accurate monitoring of the inflammatory activity after treatment [38,39*]. ^{18}F-FDG PET/CT was also found to be useful in the follow-up of LVV is a series of 37 patients with GCA. With regard to this, the mean target-to-background ratio (TBR – the aortic wall uptake divided by blood pool uptake) decreased significantly during the follow-up in the group of patients who experienced clinical improvement. However, in patients with poor clinical response, no differences were found between the initial and the follow-up TBR results [39*]. As the therapy used for the management of GCA, in particular, the use of the anti-interleukin-6 receptor tocilizumab, decreases the levels of acute phase reactants [40*,41,42*], ^{18}F-FDG PET/CT would be useful in patients with poor clinical response or suspicion of relapse after the decrease of therapy [39*].

Differences between GCA with predominant cranial pattern versus those with predominant LVV pattern

Unlike patients with GCA along with predominant cranial manifestations, patients with predominant LVV tend to be affected at a younger age. The average age is lower than 70 years, whereas it is higher in those with classic cranial manifestations of GCA. As symptoms are often noon-specific, patients with predominant LVV have longer delay to the diagnosis (often more than 3 months since the onset of symptoms), lower frequency of visual ischemic manifestations, blindness being uncommon. In contrast, these patients exhibit more commonly PMR features than those with predominant cranial GCA [43,44*]. They also have a torpid clinical course and higher frequency of relapses than those with the cranial pattern. Moreover, in patients with predominant LVV pattern, the arterial involvement of the subclavian- axillo-humeral axis and or the ilio-femoral arterial vessels may lead to intermittent limb claudication (more frequently in the upper than in the lower extremities), which is uncommon in those with the predominant cranial pattern. Hence, there is interest in the US of axillary and subclavian arteries in these patients. Table 2 shows differences in the clinical spectrum of GCA according to the predominant pattern of the disease.

Polymyalgia rheumatica is often the presenting manifestation of GCA

PMR is characterized by the presence of severe bilateral pain and stiffness involving the arms and, less commonly, the neck, the pelvic girdle, and the proximal aspects of the thighs, usually associated with increase in ESR and CRP levels in individuals older than 50 years [45*]. Patients with PMR complain of morning stiffness generally lasting for more than 45 min [45*,46]. They face problems to perform daily life activities, such as combing or dressing, which are more severe in the morning [45*,46]. Although PMR may present as an isolated condition, PMR and GCA are often overlapping conditions [45*,47,48*]. Both entities can occur simultaneously, which is the most common situation, or separated in time, so that either of them can precede the other, usually in a period ranging from several months to one or two years, although intervals of up to 9 years have been reported [45*,47,48*].

Table 2
Differences between GCA with a predominant cranial pattern and GCA with a predominant extracranial (LVV) pattern.

	Disease Pattern	
Main features	Predominant cranial	Predominant LVV
Age of disease onset	65–85 years	50–70 years
Constitutional symptoms	++	+++
Cranial ischemic manifestations	+++	+
Positive temporal artery biopsy	++	+/–
Visual ischemic complications	+	+/–
Polymyalgia rheumatica	++	++/+++
Intermittent limb claudication	+/–	+

When they are not presented simultaneously, it is usual for the PMR to appear after the diagnosis of GCA during the course of a relapse of the disease [49,50*].

A population-based study showed that both patients with isolated PMR and those with biopsy-proven GCA associated with PMR manifestations have, in most cases, elevation of the ESR. However, patients with isolated PMR have less commonly anemia, thrombocytosis, and constitutional syndrome than those with PMR associated with classic biopsy-proven GCA [51]. Also, the mean ESR was lower in patients with isolated PMR than in those with GCA associated with PMR [51].

However, less commonly, ischemic GCA manifestations may also be observed in the follow-up of patients initially diagnosed as having isolated PMR. As the initial dose of prednisone used in isolated PMR to improve symptoms is lower than that required to prevent the risk of blindness in GCA [52], clinicians should be aware of the risk of vascular arteritis features in the follow-up of patients with PMR who, at the time of disease diagnosis, did not present any apparent ischemic features of GCA. A population-based study highlighted this issue, showing relapses in patients initially diagnosed as having an isolated PMR characterized by the presence of typical cranial ischemic manifestations of GCA, including visual manifestations such as blindness, and upper extremity vascular insufficiency due to stenotic involvement of the arteries [53*]. These observations reinforce the need for a close-follow-up of patients with isolated PMR due to the frequent overlap between PMR and GCA [53*].

PMR may be the presenting feature in patients with LVV. A recent study has shown that LVV involvement is often observed in patients with persistent PMR who have inflammatory low back pain, predominant pelvic girdle, and or diffuse limb pain [54*].

Based on these observations, newly diagnosed PMR patients should be assessed for the presence of GCA. In addition to a clinical history and a thorough physical examination to identify bruits as well as cranial ischemic manifestations, a systematic assessment of the peripheral arteries should be conducted. Close monitoring of these patients with PMR should be continued over the entire course of the disease. Imaging techniques such as US and ^{18}F-FDG-PET/CT scan often disclose the presence of LVV in refractory PMR or in those with atypical PMR manifestations [54*]. In patients with PMR in whom LVV is present, we prescribe a higher dose of prednisone than that in isolated ("pure") PMR. With regard to this, in these cases, we propose to start treatment with 40 mg/prednisone/day. Fig. 4 summarizes the management of a patient presenting with polymyalgia rheumatica.

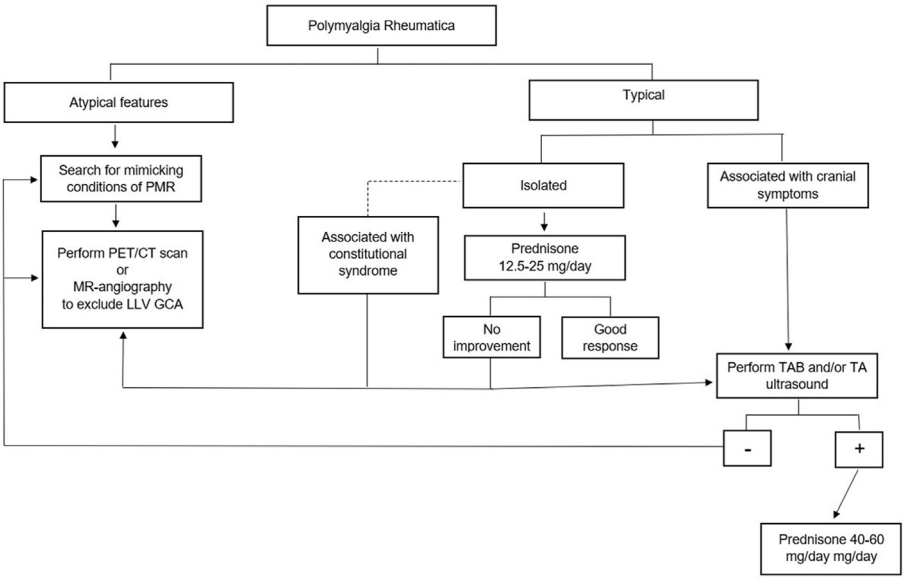

Fig. 4. Workup in the management of a patient presenting with polymyalgia rheumatica.

Summary

In addition to the typical pattern of cranial ischemic manifestations, LVV involvement has emerged as a common feature of GCA. Patients with predominant LVV features differ from those with the classic cranial pattern. They are usually affected at a younger age and often have nonspecific manifestations such as constitutional syndrome, fever of unknown origin, or refractory/atypical polymyalgia rheumatica PMR. Patients with LVV-GCA exhibit predominant extracranial features such as limb claudication, and cranial ischemic manifestations are often absent. Early diagnosis of GCA is needed in adults presenting with cranial ischemic manifestations to prevent the development of irreversible complications, mainly blindness. A high index of suspicion of GCA is also required in patients presenting with isolated PMR, as PMR is often the presenting manifestation of GCA. Patients with isolated PMR should be followed up owing to the potential risk of severe vascular complications in the setting of an underlying GCA. A close follow-up of patients with GCA is also required, as LVV involvement may occur years after initial recognition of the disease. Doppler sonography of the subclavian and axillary arteries as well as other imaging techniques such as ^{18}F-FDG-PET/CT scan, MR, or CT-angiography are very useful to identify the presence of LVV, and they may also play a role in the follow-up of these patients.

Practice points

- GCA is the most common vasculitis in individuals older than 50 years from Western countries.
- The clinical spectrum of the disease in GCA ranges from a predominance of cranial ischemic manifestations to that of an LVV pattern with extracranial features, such as limb claudication, in which cranial ischemic manifestations are often absent.
- Patients with LVV-GCA often present with nonspecific symptoms such as constitutional syndrome, fever of unknown origin, or refractory/atypical PMR.
- Early diagnosis of GCA, in particular, in patients presenting with cranial features, is required to reduce the high risk of blindness.
- PMR is often the presenting manifestation of GCA, and patients with isolated PMR should be followed up due to the potential risk of severe vascular complications in the setting of an underlying GCA.
- Whereas TAB and/or color duplex US of the temporal artery is useful for the diagnosis of cranial GCA, Doppler sonography of the subclavian and axillary arteries and other imaging techniques such as ^{18}F-FDG-PET/CT scan, MR, or CT-angiography are useful to identify LVV in the context of GCA.
- Imaging techniques such as ^{18}F-FDG-PET/CT scan may be also useful in the follow-up of these patients.

Research agenda

- Advances in the understanding of the GCA immunopathogenesis will help us to develop new strategies for an early diagnosis and management of this vasculitis.
- Development of biomarkers that allow us to identify patients with GCA soon after the occurrence of irreversible ischemic complications.
- Improving access and precision of imaging techniques to help in the diagnosis and follow-up of patients with GCA

Conflicts of interest

Dr MAG-G received grants/research supports from Abvvie, MSD, Janssen, and Roche, and had consultation fees/participation in company sponsored speaker's bureau from Abbott, Pfizer, Roche, Sanofi, Lilly, Celgene, and MSD.

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References

[1] Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1–11.
[2] Gonzalez-Gay MA, Miranda-Filloy JA, Lopez-Diaz MJ, et al. Giant cell arteritis in northwestern Spain: a 25-year epidemiologic study. Medicine (Baltim) 2007;86:61–8.
[3] Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum 2009;61:1454–61.
[4] González-Gay MA, Amoli MM, Garcia-Porrua C, et al. Genetic markers of disease susceptibility and severity in giant cell arteritis and polymyalgia rheumatica. Semin Arthritis Rheum 2003;33:38–48.
*[5] Carmona FD, Mackie SL, Martín JE, et al. A large-scale genetic analysis reveals a strong contribution of the HLA class II region to giant cell arteritis susceptibility. Am J Hum Genet 2015;96:565–80.
[6] Gonzalez-Gay MA, Barros S, Lopez-Diaz MJ, et al. Giant cell arteritis: disease patterns of clinical presentation in a series of 240 patients. Medicine (Baltim) 2005;84:269–76.
[7] González-Gay MA, García-Porrúa C, Llorca J, et al. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. Medicine (Baltim) 2000;79:283–92.
[8] Gonzalez-Gay MA, Vazquez-Rodriguez TR, Gomez-Acebo I, et al. Strokes at time of disease diagnosis in a series of 287 patients with biopsy-proven giant cell arteritis. Medicine (Baltim) 2009;88:227–35.
[9] Salvarani C, Hunder GG. Giant cell arteritis with low erythrocyte sedimentation rate: frequency of occurrence in a population-based study. Arthritis Rheum 2001;45:140–5.
[10] Gonzalez-Gay MA, Lopez-Diaz MJ, Barros S, et al. Giant cell arteritis: laboratory tests at the time of diagnosis in a series of 240 patients. Medicine (Baltim) 2005;84:277–90.
[11] Gonzalez-Gay MA. The diagnosis and management of patients with giant cell arteritis. J Rheumatol 2005;32:1186–8.
[12] Mahr A, Saba M, Kambouchner M, et al. Temporal artery biopsy for diagnosing giant cell arteritis: the longer, the better? Ann Rheum Dis 2006;65:826–8.
[13] Schmidt WA. Doppler ultrasonography in the diagnosis of giant cell arteritis. Clin Exp Rheumatol 2000;18(4 Suppl. 20): S40–2.
[14] Schmidt WA, Blockmans D. Use of ultrasonography and positron emission tomography in the diagnosis and assessment of large-vessel vasculitis. Curr Opin Rheumatol 2005;17:9–15.
*[15] Chrysidis S, Duftner C, Dejaco C, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group. RMD Open 2018;4:e000598.
*[16] Monti S, Floris A, Ponte C, et al. The use of ultrasound to assess giant cell arteritis: review of the current evidence and practical guide for the rheumatologist. Rheumatology (Oxford) 2018;57:227–35.
[17] Karassa FB, Matsagas MI, Schmidt WA, et al. Meta-analysis: test performance of ultrasonography for giant-cell arteritis. Ann Intern Med 2005;142:359–69.
*[18] Dejaco C, Ramiro S, Duftner C, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis 2018;77:636–43.
[19] Gonzalez-Gay MA, Garcia-Porrua C, Llorca J, et al. Biopsy-negative giant cell arteritis: clinical spectrum and predictive factors for positive temporal artery biopsy. Semin Arthritis Rheum 2001;30:249–56.
*[20] Germanò G, Muratore F, Cimino L, et al. Is colour duplex sonography-guided temporal artery biopsy useful in the diagnosis of giant cell arteritis? A randomized study. Rheumatology (Oxford) 2015;54:400–4.
[21] González-Gay MA, Blanco R, Rodríguez-Valverde V, et al. Permanent visual loss and cerebrovascular accidents in giant cell arteritis: predictors and response to treatment. Arthritis Rheum 1998;41:1497–504.
*[22] Gonzalez-Gay MA, Castañeda S, Llorca J. Giant Cell Arteritis: visual loss is our major concern. J Rheumatol 2016;43: 1458–61.
[23] Pipitone N, Versari A, Hunder GG, et al. Role of imaging in the diagnosis of large and medium-sized vessel vasculitis. Rheum Dis Clin N Am 2013;39:593–608.
*[24] Salvarani C, Soriano A, Muratore F, et al. Is PET/CT essential in the diagnosis and follow-up of temporal arteritis? Autoimmun Rev 2017;16:1125–30.
[25] Fuchs M, Briel M, Daikeler T, et al. The impact of 18F-FDG PET on the management of patients with suspected large vessel vasculitis. Eur J Nucl Med Mol Imaging 2012;39:344–53.
[26] Martínez-Rodríguez I, Martínez-Amador N, Banzo I, et al. Assessment of aortitis by semiquantitative analysis of 180-min 18F-FDG PET/CT acquisition images. Eur J Nucl Med Mol Imaging 2014;41:2319–24.
*[27] Löffler C, Hoffend J, Benck U, et al. The value of ultrasound in diagnosing extracranial large-vessel vasculitis compared to FDG-PET/CT: a retrospective study. Clin Rheumatol 2017;36:2079–86.
*[28] Schäfer VS, Juche A, Ramiro S, et al. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. Rheumatology (Oxford) 2017;56:1479–83.

[29] Nuenninghoff DM, Hunder GG, Christianson TJ, et al. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. Arthritis Rheum 2003;48:3522–31.
[30] Gonzalez-Gay MA, Garcia-Porrua C, Piñeiro A, et al. Aortic aneurysm and dissection in patients with biopsy-proven giant cell arteritis from northwestern Spain: a population-based study. Medicine (Baltim) 2004;83:335–41.
[31] Nuenninghoff DM, Hunder GG, Christianson TJ, et al. Mortality of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. Arthritis Rheum 2003;48:3532–7.
*[32] Kermani TA, Diab S, Sreih AG, et al. Arterial lesions in giant cell arteritis: a longitudinal study. Semin Arthritis Rheum 2019;48:707–13.
[33] Gonzalez-Gay MA, Garcia-Porrua C, Amor-Dorado JC, et al. Fever in biopsy-proven giant cell arteritis: clinical implications in a defined population. Arthritis Rheum 2004;51:652–5.
[34] Gonzalez-Gay MA, Garcia-Porrua C, Amor-Dorado JC, et al. Giant cell arteritis without clinically evident vascular involvement in a defined population. Arthritis Rheum 2004;51:274–7.
[35] Brack A, Martinez-Taboada V, Stanson A, et al. Disease pattern in cranial and large-vessel giant cell arteritis. Arthritis Rheum 1999;42:311–7.
[36] Blockmans D, Bley T, Schmidt W. Imaging for large-vessel vasculitis. Curr Opin Rheumatol 2009;21:19–28.
*[37] Muratore F, Kermani TA, Crowson CS, et al. Large-vessel giant cell arteritis: a cohort study. Rheumatology (Oxford) 2015;54:463–70.
[38] Loricera J, Blanco R, Hernández JL, et al. Use of positron emission tomography (PET) for the diagnosis of large-vessel vasculitis. Rev Esp Med Nucl Imagen Mol 2015;34:372–7.
*[39] Martínez-Rodríguez I, Jiménez-Alonso M, Quirce R, et al. ^{18}F-FDG PET/CT in the follow-up of large-vessel vasculitis: a study of 37 consecutive patients. Semin Arthritis Rheum 2018;47:530–7.
*[40] Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med 2017;377:317–28.
[41] Loricera J, Blanco R, Hernández JL, et al. Tocilizumab in giant cell arteritis: multicenter open-label study of 22 patients. Semin Arthritis Rheum 2015;44:717–23.
*[42] Calderón-Goercke M, Loricera J, Aldasoro V, et al. Tocilizumab in giant cell arteritis. Observational, open-label multicenter study of 134 patients in clinical practice. Semin Arthritis Rheum 2019 Jan 5. pii: S0049-0172(18)30571-30577.
[43] Loricera J, Blanco R, Hernández JL, et al. Non-infectious aortitis: a report of 32 cases from a single tertiary centre in a 4-year period and literature review. Clin Exp Rheumatol 2015;33(2 Suppl. 89):S19–31.
*[44] Koster MJ, Matteson EL, Warrington KJ. Large-vessel giant cell arteritis: diagnosis, monitoring and management. Rheumatology (Oxford) 2018;57(Suppl. 2):ii32–42.
*[45] González-Gay MA, Matteson EL, Castañeda S. Polymyalgia rheumatica. Lancet 2017;390:1700–12.
[46] Dasgupta B, Cimmino MA, Kremers HM, et al. 2012 Provisional classification criteria for polymyalgia rheumatica: a European League against Rheumatism/American College of Rheumatology Collaborative Initiative. Arthritis Rheum 2012;64:943–54.
[47] Gonzalez-Gay MA. Giant cell arteritis and polymyalgia rheumatica: two different but often overlapping conditions. Semin Arthritis Rheum 2004;33:289–93.
*[48] González-Gay MA, Pina T, Prieto-Peña D, et al. Current and emerging diagnosis tools and therapeutics for giant cell arteritis. Expert Rev Clin Immunol 2018;14:593–605.
[49] Martinez-Lado L, Calviño-Díaz C, Piñeiro A, et al. Relapses and recurrences in giant cell arteritis: a population-based study of patients with biopsy-proven disease from northwestern Spain. Medicine (Baltim) 2011;90:186–93.
[50] Castañeda S, García-Castañeda N, Prieto-Peña D, et al. Treatment of polymyalgia rheumatica. Biochem Pharmacol 2019 Mar 20. https://doi.org/10.1016/j.bcp.2019.03.027. pii: S0006-2952(19)30113-3.
[51] González-Gay MA, García-Porrúa C, Vázquez-Caruncho M. Polymyalgia rheumatica in biopsy proven giant cell arteritis does not constitute a different subset but differs from isolated polymyalgia rheumatica. J Rheumatol 1998;25:1750–5.
[52] Salvarani C, Cantini F, Boiardi L, et al. Polymyalgia rheumatica and giant-cell arteritis. N Engl J Med 2002;347:261–71.
*[53] Narvaez J, Estrada P, López-Vives L, et al. Prevalence of ischemic complications in patients with giant cell arteritis presenting with apparently isolated polymyalgia rheumatica. Semin Arthritis Rheum 2015;45:328–33.
*[54] Prieto-Peña D, Martínez-Rodríguez I, Loricera J, et al. Predictors of positive (18)F-FDG PET/CT-scan for large vessel vasculitis in patients with persistent polymyalgia rheumatica. Semin Arthritis Rheum 2019;48:720–7.