Editorial

Giant cell arteritis: more than a cranial disease

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Giant cell arteritis (GCA) is a systemic vasculitis of large and medium-sized arteries in patients aged over 50 years (1, 2). Classic reports defined GCA as a vasculitis presenting a typical clinical picture consisting of cranial ischaemic manifestations. Due to this, GCA was also termed as "temporal" arteritis (3, 4). However, step by step, clinicians reported atypical features (5) and also emphasised the problems to make a diagnosis of GCA in the absence of cardinal cranial manifestations (6, 7). In this context, the presence of extracranial features of GCA has become more and more evident. In this regard, several studies highlighted the relevance of the involvement of the aorta and its major branches leading to an increased incidence of aortic aneurysms and dissection in GCA patients (8, 9). In keeping with that, a review of 72 cases of aortic and extracranial GCA showed that 25% of patients with aortic and extracranial large-vessel GCA had asymptomatic temporal arteritis (10). These patients had more commonly involvement of the ascending aorta and aortic arch, followed by the subclavian and humero-axillary arteries, and the femoropopliteal arteries. Of note, 9 of these 72 patients suffered upper or lower limb amputation (10).

An elegant study conducted by Brack *et al*. compared the clinical manifestations of 74 patients with subclavian/axillary GCA diagnosed by angiography with those of 74 patients with biopsy-proven GCA presenting with the typical pattern of the cranial "temporal" arteritis without large-vessel involvement (11). Patients with large-vessel GCA had commonly upper extremity vascular insufficiency whereas cranial ischaemic manifestations were uncommon. Moreover, temporal artery biopsy findings were negative in 42% of the patients with large-vessel GCA (11). These findings supported the claim that GCA with predominant large-vessel involvement has a different clinical spectrum of the disease, often presenting without clinically evident cranial ischaemic manifestations.

In line with the above, a recent prospective, longitudinal, multi-center study that included 187 GCA patients with cranial or large-vessel vasculitis features showed that two thirds of the patients had at least one arterial lesion on first imaging study. The most frequently observed locations of vascular lesions in decreasing frequency were observed in the subclavian (42%), axillary (32%), and thoracic aortic (20%) arteries (12). New vascular lesions on serial imaging during the follow-up were more commonly observed in patients with a diagnosis of GCA based on large-scale vasculitis assessment (12). These observations gave support to the use of imaging techniques to identify the presence of extracranial large-vessel involvement at the time of GCA diagnosis and also during the follow-up.

Muratore *et al*. compared the clinical spectrum of manifestations of 120 GCA patients with large-vessel GCA primarily of the upper extremities with those of 212 GCA patients who presented with the classic cranial pattern of the disease (13). GCA patients with predominant large-vessel involvement were younger, had a longer delay to the diagnosis and more commonly polymyalgia rheumatica (PMR) than those with the classic cranial phenotype. Moreover, patients with predominant large-vessel involvement had less commonly visual loss but experienced more relapses and required longer glucocorticoid therapy (13).

Since cranial manifestations may be absent or they may not represent the major point of complain of some patients

Table I. Differences in the clinical spectrum of the disease between GCA patients with predominant cranial (temporal) pattern and those with predominant extracranial large-vessel vasculitis pattern.

	Pattern of the disease	
	Predominant cranial	Predominant LVV
Age at disease onset	65-85 years	50-70 years
Delay to diagnosis: longer duration	+	++
Constitutional symptoms	++	+++
Cranial ischaemic manifestations	+++	+
Positive temporal artery biopsy	++	+/-
Visual ischaemic complications	+/++	+/-
Polymyalgia rheumatica	++	++/+++
Intermittent limb claudication	+/-	+
Relapses	+/++	++
Glucocorticoid therapy: longer duration	++	+++

GCA: giant cell arteritis; LVV: large-vessel vasculitis.

with GCA, extra-cranial large-vessel GCA is still a diagnostic challenge unless local ischaemic manifestations appear (14). The high frequency of PMR in patients with extracranial-large-vessel GCA pointed out by Muratore *et al*. (13) constitutes another potential point of concern since PMR is also a common condition in patients older than 50 years (1), and it may present as an isolated condition of associated with GCA (15). Although an epidemiologic study indicated that patients with isolated PMR had lower frequency of constitutional syndrome, lower elevation of erythrocyte sedimentation rate and platelet counts and higher values of haemoglobin than those with PMR associated with biopsy-proven GCA (16), there are not well defined clinical tools that may help to identify an "occult" GCA in patients presenting as a "pure" (isolated) PMR. Nevertheless, the greater accessibility to new vascular imaging techniques, including angio-magnetic resonance imaging (MRI)/computed-tomography (CT), ultrasonography and fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) scan, has allowed us to identify the presence of large-vessel vasculitis in patients presenting with typical or atypical PMR (17, 18). With respect to this, large-vessel vasculitis involvement is often observed in patients with persistent PMR who have inflammatory low back pain, predominant pelvic girdle and or diffuse limb pain (19). On the other hand, although most patients with a recent diagnosis of temporal-artery-biopsy-proven GCA do not show clinical evidence of vascular ischaemic manifestations (6, 7), imaging techniques such as angio-CT/angio-MRI or PET/CT scan often disclose the presence of an asymptomatic extra-cranial vascular large-vessel vasculitis involvement (18, 20, 21). These findings demonstrate that GCA involves vessels far beyond the temporal and other cranial arteries (20, 21). Therefore, clinicians should be aware of the potential relevance 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.

Table I summarises the main clinical differences between GCA presenting with a predominant classic "temporal"-cranial phenotype of GCA and those with a predominant extracranial large-vessel vasculitis pattern.

In conclusion, GCA is an inflammatory disease with very heterogeneous and sometimes non-specific clinical manifestations that can lead to inappropriate delay to the diagnosis. Higher awareness of clinical presentations different from the classic pattern of cranial manifestations may reduce the risk of serious complications such as arterial ischaemia and acute aortic syndromes. Finally, close follow-up of GCA looking for extracranial vascular complications is also required since large-vessel involvement may occur years after initial recognition of the disease.

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