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Review

The spectrum of giant cell arteritis and polymyalgia rheumatica: revisiting the concept of the disease

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Abstract

GCA and PMR are conditions of older persons that frequently overlap. The traditional concept of GCA has focused on cranial symptoms such as headache and visual disturbance, but extra-cranial manifestations such as constitutional symptoms, polymyalgia and limb claudication have also long been recognized. These symptoms may coincide with cranial GCA, occur as an independent clinical subset [large-vessel (LV) GCA] or overlap with PMR. Imaging studies have demonstrated that up to one-third of patients with PMR have subclinical LV inflammation at disease outset. The implication of this finding for PMR management is unclear. Pathophysiological studies have emphasized the pivotal role of dendritic cells (DCs) and T cells in the pathogenesis of GCA, and the activation of certain pattern recognition receptors on DCs may determine the clinical subset of GCA. In patients with only PMR clinically, it is conceivable that transmural arterial inflammation has either not yet started or is prevented by unexplored regulatory pathways. This concept is supported by vasculitis of peri-adventitial small-vessels and activated DCs in the adventitia of temporal arteries, in the absence of media-infiltrating T cells. This review examines the clinical and pathophysiological spectrum of GCA and its subsets with PMR, the role of newer imaging techniques for GCA diagnosis and the management of these diseases.

Key words: giant cell arteritis, polymyalgia rheumatica, diagnostic imaging, immunosuppressants, biological therapies, vasculitis

REVIEW

Rheumatology key messages

- GCA is a clinical syndrome encompassing cranial and extra-cranial arteritis as well as PMR.
- PMR patients with inadequate response and/or recurrent relapses should be evaluated for an alternative diagnosis and management plan.
- GCA and PMR are treated with glucocorticoids; methotrexate may be used in individual cases.

Introduction

GCA and PMR are inflammatory rheumatic disorders occurring almost exclusively in older persons, with the highest incidence found in Scandinavian countries and people of northern European descent [1, 2]. The spectrum of GCA encompasses overlapping phenotypes including classic cranial arteritis and extra-cranial GCA, also referred to as large-vessel GCA (LV-GCA). LV vasculitis linked to other systematic diseases such as Behçet's disease or hyper-IgG4 syndrome is not within the scope of this review [3]. It is unknown whether single-organ vasculitis of the aorta or a single large artery (e.g. carotids) in the elderly might be considered as a limited expression of LV-GCA or whether it represents true single-organ vasculitis. The latter has been classified as a distinct vasculitis entity by the 2012 revised International Chapel Hill Consensus Conference [4].

GCA and PMR commonly overlap. PMR is observed in 40–60% of patients with GCA at diagnosis, and 16–21% of patients with PMR may develop GCA, particularly if left untreated [2]. Modern imaging studies using vascular US and/or 18-fluorine fluorodeoxyglucose PET/CT (^{18}F-FDG PET) have demonstrated that at diagnosis, up to 80% of

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GCA patients as well as one-third of patients with PMR have subclinical LV inflammation. Patients with treatment refractory PMR commonly have cranial and/or extracranial arteritis on imaging [5–11].

This review examines the phenotypic overlap between the different GCA subtypes and PMR, the role of new imaging techniques for GCA diagnosis, as well as the evidence for a common pathophysiology of GCA and PMR and implications of GCA/PMR overlap for disease management. We also propose an extension of the 1990 classification criteria for GCA toward the inclusion of cranial and extracranial symptoms and signs as well as imaging results.

GCA beyond temporal arteritis—tracks from history to modern times

As early as in 1932, when Bayard Horton made his original description of two cases of temporal arteritis, he stressed the fact that these patients suffered from a systemic constitutional syndrome associated with temporal artery inflammation. Interestingly, one of these cases had a missing radial pulse, suggesting LV-GCA [12]. In 1960, Paulley and Hughes [13] reported on a clinical subset of GCA labelled as anarthritic rheumatism, corresponding to PMR, in which the classical stigmata of GCA have yet to develop, or have already occurred. The term polymyalgia arteritica was introduced in 1972 by Hamrin, recognizing that many cases with phenotypic PMR had arteritis on temporal artery biopsy [14]. The practice of categorizing patients with PMR under the umbrella of GCA continues in Scandinavia to the present. In 1990, the ACR Classification Criteria Committee aimed to distinguish GCA from other forms of vasculitis. Headache was identified as an important differentiating feature [15]. Unfortunately, these criteria have been misused as diagnostic criteria, leading to the mistaken widespread understanding of GCA as primarily a headache disease omitting key constitutional, polymyalgic and major organ threatening features such a jaw pain, visual symptoms and vision loss.

The concept of GCA as a clinical syndrome comprising cranial GCA, LV-GCA and PMR has recently had a renaissance, appreciated in the context of new clinical trials in GCA. GIACTA, a trial of tocilizumab in GCA (ClinicalTrials.gov Identifier: NCT01791153), SIRRESTA, a study of sirukumab in GCA (NCT02531633) and a study on gevokizumab in GCA (EudraCT Number: 2013-002778-38; prematurely closed after the agent failed its primary end point in Behçet's disease) have all included patients with polymyalgic symptoms and/or LV-GCA, as long as GCA diagnosis was supported by either biopsy or appropriate imaging results. Publication of these trials is expected in the near future.

GCA: a clinical syndrome

Cranial GCA, LV-GCA and PMR as phenotypically overlapping conditions

The most common clinical signs and symptoms observed in cranial and LV-GCA as well as in PMR are listed in Table 1. Figure 1 illustrates the phenotypic overlap between these diseases and depicts characteristic imaging examples.

Table 1 Clinical symptoms and signs in subtypes of GCA and PMR

Symptoms and signs	Cranial GCA	LV-GCA	PMR
Headache	++	−	−
Arterial swelling/tenderness, bruits	+	+	−
Jaw claudication/tongue pain	++	−	−
Visual symptoms/complications	++	−	−
Fever, weight loss	+	++	++
Arm claudication, RP	+	++	−
Polymyalgic symptoms	+	++	++
Acute phase reactants	++	++	++
Peripheral arthritis/RS3PE syndrome	+	+	++

++: very common symptom/sign; +: common; −: uncommon. LV: large-vessel; RS3PE: remitting seronegative symmetric synovitis with pitting oedema.

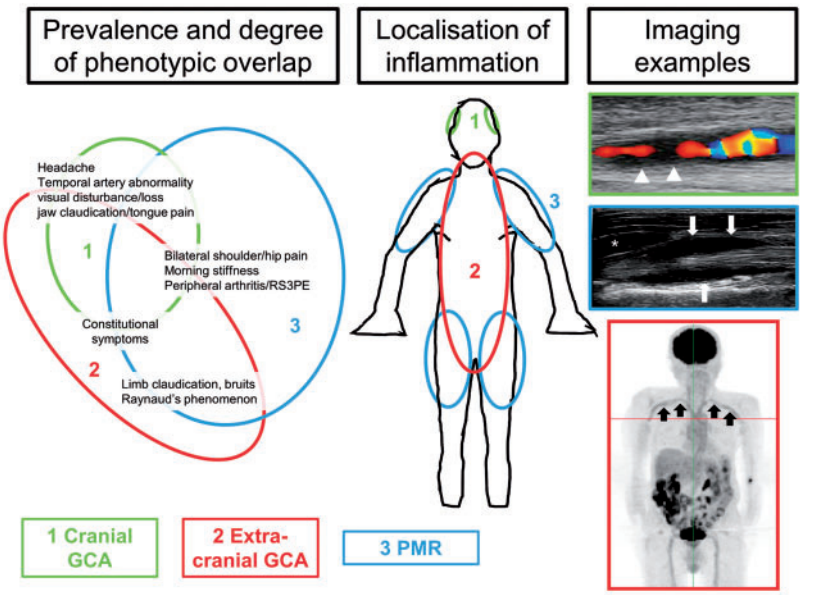
The traditional description of GCA has focused on cranial symptoms, particularly headache and swelling and/or tenderness of the temporal artery as embodied in the 1990 ACR classification criteria for GCA [15]. Accordingly, the combination of any three out of five criteria (age $\geqslant$50 years, new headache, clinical temporal artery abnormality, ESR $\geqslant$50 mm/1 h and positive temporal artery biopsy) resulted in a >90% sensitivity and specificity for GCA classification *vs* other forms of vasculitis [15].

Epidemiological studies have demonstrated that two-thirds of patients with cranial GCA complain about new headache [16]. Other cranial symptoms such as visual disturbance (~20–30%), jaw claudication (~50%) and tongue pain are less common but if present increase the likelihood for GCA diagnosis [17, 18].

In the past, loss of vision was reported in 15–35% of patients with GCA. However in recent years, the risk of visual complications has been much lower, likely due to increased recognition of the disease, prompt initiation of therapy and the introduction of fast-track GCA clinics [18, 19]. Blindness in GCA is permanent and may be preceded by amaurosis fugax, diplopia, tongue pain or tongue necrosis and/or jaw claudication [20]. The absence of these symptoms, however, does not preclude the occurrence of visual complications; rather we have recently observed that patients with sight loss reported transient visual symptoms and headache less frequently than patients without visual complications [18]. These patients were older, more commonly men and more frequently had hypertension as well as a positive temporal artery biopsy result.

Untreated patients with unilateral visual loss have a 50% risk of blindness in the other eye, usually occurring after a few days [20, 21]. Less common ischaemic

FIG. 1 Disease spectra of cranial, large-vessel GCA and PMR



Left: prevalence and phenotypic overlap. The size of the circles reflects the estimated incidence of each condition (relative to each other, not indicating absolute values), and the overlapping areas correspond to the proportion of the phenotypic overlap. At the crossing of the curves, characteristic clinical symptoms of the respective diseases are depicted. Middle: main localization of inflammation in each disease. Right: imaging findings. Green box: US image of a patient with cranial GCA showing the halo sign (arrowhead). Blue box: US image of a PMR patient. White arrows point to biceps tenosynovitis, the asterix depicts subdeltoid bursitis. Red box: ^{18}F-FDG PET image of a patient with large-vessel-GCA. Black arrows indicate FDG uptake in supra-aortic large arteries.

complications of GCA include cerebrovascular strokes, infarction of the tongue and scalp necrosis [2].

Up to half of patients with cranial GCA may present with constitutional symptoms such as fever, malaise, depression, anorexia and weight loss. These symptoms may be the dominant clinical manifestations in about 15% of patients at presentation, and in 20% of cases at time of relapse [22–25]. Patients with LV-GCA also commonly suffer from constitutional symptoms, and at least 10% of patients with LV-GCA have been evaluated for fever of unknown origin [8, 26]. GCA-related fever is usually low-grade, but may sometimes reach 39–40°C. It is caused by a strong systemic acute phase response and the release of pro-inflammatory and fever-generating cytokines such as IL-6 and IL-1 [1].

The most common extra-cranial clinical manifestation of GCA is PMR, occurring in 45–61% of patients at time of diagnosis [8, 27, 28]. PMR is the most frequent symptom of relapse (~50%) in GCA, whereas headache and other cranial manifestations (31–42%) are less frequent [24, 29].

Other symptoms at presentation of LV-GCA may include intermittent arm/limb claudication and back or chest pain (due to aortitis or aortic dissection). RP or peripheral neuropathic syndromes are less common [8, 30–32]. Acute phase reactant levels are usually raised in these cases, and imaging reveals inflammation of the arteries in the proximal upper and/or lower limbs and/or the aorta [33, 34]. The latter symptoms resemble Takayasu arteritis; however, patients with GCA are older, present more acutely, rarely have involvement of visceral arteries (such as mesenteric or renal) and almost never have stenosis/occlusion of the aorta [35]. Conversely, aortic aneurysms are far more common in GCA than in Takayasu's disease [36].

Recent imaging studies suggest that in patients with cranial GCA, large arteries are more commonly involved than suspected on clinical grounds, particularly in patients with a strong acute phase response and/or systemic complaints [5, 9, 37–39]. In patients with relapsing PMR,[18] F-FDG PET scans performed in re-evaluation of diagnosis frequently demonstrate tracer uptake in large vessels and/or the aorta, prompting the treating physician to revise the diagnosis toward GCA [7, 40].

A high prevalence of ischaemic complications was reported in a retrospective study of patients developing GCA on the background of established PMR [41]. In other studies, however, ischaemic complications were rare once GCs have been initiated and clinical symptoms resolved [38]. Recognizing the frequent PMR-GCA overlap and PMR mimics, the 2015 EULAR–ACR PMR recommendations suggest re-evaluation of PMR diagnosis in every case with inadequate response to GCs and/or relapse(s) including imaging of large arteries [42, 43].

Overlap between GCA, PMR and inflammatory arthropathies in older persons

There is a high prevalence of peripheral musculoskeletal manifestations in GCA and PMR including peripheral

arthritis, distal extremity swelling with pitting oedema (RS3PE), tenosynovitis and/or carpal tunnel syndrome occurring in up to 25 and 50% of patients, respectively [44–46]. Synovitis is typically non-erosive, presenting as mono-, oligo- or polyarthritis. RS3PE is characterized by symmetric swelling of hands and/or feet with pitting oedema and is typically associated with PMR and rarely with GCA [47]. RS3PE may also occur in the context of other inflammatory (e.g. RA) and non-inflammatory conditions (e.g. neoplasia). Meticulous exclusion of other diagnoses is necessary if patients present with polymyalgia and RS3PE [48, 49].

Several rheumatic conditions can cause a polymyalgic syndrome of proximal pain and stiffness in older persons. In clinical practice, it may therefore be challenging to differentiate peripheral arthritis as a manifestation of PMR from inflammatory arthropathies with a polymyalgic onset including elderly onset RA (EORA, in whom myalgia occurs in 16% of cases), elderly onset spondyloarthritis or crystal arthropathies. There is no specific test for PMR, and US results may be similar in PMR and EORA patients [50]. Up to 30% of cases with inflammatory arthropathies (particularly EORA) are thus misclassified as PMR [51].

The frequent phenotypic overlap between PMR and EORA has also provoked recurrent debates about a possible common disease entity of PMR and RA (rather than of PMR and GCA) [52]. Results from imaging and pathophysiological studies, however, argue against this hypothesis: first, MRI and ^{18}F-FDG PET reveal different patterns of joint and periarticular inflammation in PMR and RA, and inflammation of large vessels is not a feature of RA [5, 53–55]. Second, key elements of RA pathogenesis are the production of autoantibodies, particularly against citrullinated proteins (as measured by anti-CCP assays) and the Fc fragment of IgG (RF), as well as the inflammatory degradation of cartilage. In PMR, neither autoantibodies nor cartilage destruction occurs; however, a mild synovial infiltrate may be observed at affected sites. Inflammatory cells are present in the adventitia of large arteries of patients with PMR (but not RA), causing a strong systemic inflammatory response with a GCA-like cytokine profile [56–60]. Third, decreased numbers of circulating B cells have been observed in patients with untreated PMR and GCA, whereas the involvement of B cells is pivotal for the pathogenesis of RA [61].

Pathophysiological overlap between GCA subtypes and PMR

The current understanding of GCA is of a granulomatous autoimmune vasculitis affecting larger arteries and the aorta. The pathology of PMR (and its possible overlap with GCA) is less clear because of a paucity of histological data.

People with a certain genetic background (such as female sex, northern European descent and other genetic variants) are more susceptible than others. Genetic factors might also influence the phenotype and course of GCA and PMR. For example, a strong association between *HLA-DRB1**04 and GCA has been repeatedly observed, whereas the linkage between *HLA-DRB1* alleles and PMR is less obvious [62–66]. Polymorphisms of genes encoding cytokines (e.g. TNF-α, IL-6), chemokines and adhesion molecules [e.g. chemokine (C-C motif) ligand 5 L (CCL-5), intercellular adhesion molecule 1] as well as regulators of the innate immunity [e.g. Toll-like receptor (TLR)-4, Fc-γ receptors] were also linked to an increased susceptibility to GCA and/or PMR, although the strength of association differs between clinical subsets of GCA, and PMR [67]. Apart from genetic factors, age-related changes of the immune system and vascular tissue as well as unknown exogenous or endogenous trigger(s) may contribute to GCA/PMR pathogenesis causing an inadequate inflammatory response involving both the innate and the adaptive immune system [68].

The abnormal maturation of vascular dendritic cells (DCs) naturally residing and maintaining tolerance in the adventitia of human macrovessels is deemed the crucial event initiating and sustaining GCA [69, 70]. Activated DCs promote recruitment of T cells in the arterial wall, which eventually polarize into IFN-γ-producing Th1 and IL-17 producing Th17 cells [68]. These cytokines activate macrophages, enable formation of giant cells and promote proliferation of vascular smooth muscle cells, ultimately leading to luminal occlusion [68]. Macrophages infiltrating the adventitia releasing IL-1β and IL-6 cause a systemic inflammatory response that results in constitutional symptoms and PMR-related musculoskeletal complaints [71, 72]. T cells frequently form a ring along the internal elastic lamina, while the bulk of inflammation is localized at the border between the media and adventitia [73]. Interestingly, GC treatment rapidly disrupts Th17 responses by suppressing IL-1β, IL-6 and IL-23 whereas IFN-γ-producing Th1 cells are more resistant to immunosuppression [68, 74].

Histological studies in PMR reveal activated DCs in the adventitia of temporal arteries, and yet media-infiltrating T cells are absent [60]. Focal, peri-adventitial small-vessel vasculitis has been reported in patients with PMR, with mononuclear infiltrates surrounding capillaries distant from the non-inflamed temporal artery [75]. PCR analyses of temporal arteries from patients with GCA and PMR demonstrated a similar cytokine profile with *in situ* production of IL-1β, IL-2 and TGF-β; however, IFN-γ mRNA, characteristic for GCA, was absent in PMR samples [76].

The mechanisms preventing transmural arterial inflammation in a proportion of patients with GCA and PMR are insufficiently understood. Apart from genetic factors as detailed above, DC may play a role. Vascular DCs are equipped with a broad portfolio of pattern-recognition receptors, including TLRs, which are highly conserved molecules recognizing bacterial and viral structures as well as endogenous danger signals [77]. Although several TLRs may induce DC maturation, the cellular response is receptor specific. In a human temporal artery–SCID mouse chimera model, it has been observed that the ligation of TLR4 (by lipopolysaccharides or HSPs) caused transmural panarteritis, whereas activation of TLR5 (e.g. by bacterial flagellin) led to a limited adventitial peri-vasculitis [78].

Studies of other immune-mediated diseases reveal that Th17 cells possess the plasticity to differentiate into (IFN-γ producing) Th1 or Treg-like phenotypes [79, 80]. Given that IL-17 expression levels are linked with the intensity of the systemic inflammatory response in GCA, it is tempting to speculate that signals tipping the balance between Th17, Th1 and Tregs might determine the clinical presentation of GCA including co-occurrence of PMR [81].

Other factors potentially limiting the extent of arterial inflammation are the expression of IL-10, a cytokine known to inhibit inflammatory responses, and the recruitment of naturally occurring Tregs (nTregs) into the arterial wall [82, 83]. nTregs down-regulate innate and adaptive immune responses, but were virtually absent in temporal artery lesions from patients with GCA [84]. Whether in PMR (and other forms of aborted vasculitis) a small number of nTregs interacts with maturated DCs and/or other inflammatory cells in the adventitia of large arteries is yet to be investigated.

Another unresolved question is why GCA involves some arteries while sparing others, resulting in cranial and LV-GCA phenotypes. One possible explanation is that the equipment of DCs with TLRs is specific for a vascular bed. TLR ligands may thus induce DC activation and inflammation in certain vessels whereas others remain unaffected [68]. Whether other local factors, such as the composition of vascular stromal cells or matrix proteins, also play a role remains to be clarified [68].

Synovial inflammatory infiltrates in PMR are mainly composed of memory T cells and monocytes [85]. It is not known whether these cells recognize an antigen expressed in the synovial tissue or have been primed in large arteries (or elsewhere) and are then recruited into the synovium.

In peripheral blood, similar abnormalities in patients with GCA and PMR have been observed including an increased prevalence of senescent T cells, reduced levels of nTregs, increased numbers of Th17 lymphocytes as well as a reduction of B-cells, which normalized after introduction GC therapy [61, 84, 86, 87].

All these studies allow indirect conclusions about a possible common pathophysiology of PMR, cranial and LV-GCA. It is conceivable that PMR is a limited or aborted form of GCA in which overt vasculitis has either not yet started or has been prevented by unclear regulatory mechanisms. Pattern recognition receptors and other factors may also contribute to the clinical manifestations of GCA as predominant cranial or extra-cranial disease; however, convincing evidence supporting this concept is still lacking. Unfortunately, vascular and synovial tissue from patients with isolated PMR and vascular specimens from patients with LV-GCA are rarely obtained, and there is no established animal model to directly study the pathogenesis of these conditions [68].

Modern imaging methods in the assessment of GCA

Role of imaging for the assessment of cranial GCA

Imaging methods are increasingly used for the diagnosis of GCA [2]. Colour-duplex US, for example, can be applied to assess vascular inflammation of the temporal and other large arteries. A typical finding is the halo sign, that is, a hypoechoic ring around the arterial lumen reflecting the inflammation-induced oedematous thickening of the arterial wall [88]. In patients with suspected cranial GCA, US of temporal arteries has yielded sensitivities and specificities ranging from 55 to 100% and 78 to 100%, respectively [88–93]. High resolution MRI is an alternative to sonography to evaluate cranial GCA, with similar sensitivity (68–89%) and specificity (73–97%) [94–97]. MRI also enables the investigation of intracranial vessels revealing moderate sensitivity (50%) but high specificity (100%) for GCA diagnosis [98]. ^{18}F-FDG PET cannot be used to assess cranial GCA due to the proximity of the brain.

US, MRI and ^{18}F-FDG PET for the evaluation of LV-GCA

In patients with cranial GCA, extra-cranial arteries are also commonly affected as demonstrated by US, MRI and ^{18}F-FDG PET studies [8, 11, 99]. US examination of extra-cranial arteries increases the diagnostic yield for GCA, and the presence of US verified LV-GCA negatively correlates with visual complications [8, 100]. Imaging may be of great value for patients with suspected GCA but without classic cranial manifestations, as well as for cases of treatment-refractory PMR. In these patients, temporal artery biopsy is not routinely performed or when it is, the biopsy result may be non-diagnostic [101, 102].

The best imaging method for the investigation of LV-GCA is as yet undefined. Data from systematic reviews suggest a similar performance of US, MRI and ^{18}F-FDG PET for GCA diagnosis, but a direct comparison between all three techniques has so far not been performed [103, 104]. Diagnostic studies of LV-GCA are further limited by the fact that one imaging method is usually required to verify the presence of vasculitis (thus serving as the gold standard).

MRI and US have been compared directly for the diagnosis of cranial GCA, and have similar sensitivities (69 and 67%, respectively) and specificities (91 and 91%, respectively) using the 1990 ACR criteria assessed at baseline and after 6 months as the gold standard [105]. MRI, and to a limited extent ^{18}F-FDG PET, may be more useful than sonography for the assessment of the aorta and its branches given that some of these vessels are either not, or only insufficiently, accessible by sonography.

MRI and ^{18}F-FDG PET have been investigated for the assessment of aortitis in a study of 25 patients with complicated courses of GCA, yielding comparable sensitivities of 88 and 80%, respectively [106]. A direct comparison of US and ^{18}F-FDG PET found a similar sensitivity for detecting (any) extra-cranial involvement of GCA; however, ^{18}F-FDG PET had limited specificity to detect vasculitis of the lower limb because concomitant arteriosclerosis frequently caused false-positive results at this site [107].

Management of PMR, GCA and overlapping conditions

Current EULAR and British Society of Rheumatology (BSR) recommendations for GCA management suggest immediate treatment of GCA using GCs at a dose of 1 mg/kg (up to a maximum of 60 mg/day) or 40–60 mg/day prednisone equivalent, respectively, in order to prevent ischaemic complications, particularly blindness [108, 109]. Patients presenting early after the onset of visual symptoms may require GC pulse therapy with 0.5–1 g methylprednisolone for 3–5 days. EULAR recommends considering MTX in every GCA patient, whereas BSR has reserved this treatment for relapsing patients. According to the recently published 2015 EULAR–ACR recommendations for PMR, the initial GC dose is 12.5–25 mg/day prednisone equivalent followed by gradual dose tapering [42, 43]. MTX may be used in patients at risk of relapse and/or GC-related adverse events. BSR recommends an initial GC dose of 15 mg/day for PMR, and the introduction of MTX after the second relapse [110].

Patients with GCA and PMR symptoms, patients with GCA who have systemic manifestations as well as patients with LV-GCA usually receive the same high-dose GC regimen as patients with pure cranial GCA, with the rationale that they are considered to be at a similar risk of vascular complications compared with patients with cranial GCA [18].

There is considerable uncertainty over whether patients with PMR who have subclinical LV inflammation should be treated as having PMR or GCA. As detailed above, about 10 and 30% of patients with pure PMR may have evidence of vasculitis on US or ^{18}F-FDG PET, respectively [5, 9]. This raises the issue of whether patients with PMR should be screened with imaging for evidence of LV disease. The fact that between ~20 and ~50% of patients with PMR have an inadequate response to initial GC therapy and/or relapse within the first year may reflect the possibility that at least some of them may suffer from subclinical GCA. This is because high initial and/or persistently elevated acute phase reactants are associated with both an increased relapse risk and a higher probability for the presence of subclinical vasculitis [6, 111, 112].

The strongest argument against this hypothesis is the fact that in an ^{18}F-FDG PET study there was no increased relapse risk in patients with PMR who had subclinical LV inflammation [8]. In addition, these patients had a low risk of ischaemic complications, similar to patients with PMR who did not have vasculitis [5]. Further research is necessary before definite conclusions about the relevance of subclinical vasculitis for management of patients with PMR can be drawn. Subgroup analyses from GiACTA, SIRRESTA and gevokizumab trials including patients with polymyalgic symptoms and imaging based evidence of LV vasculitis may shed light on this issue.

Table 2 Proposal for expansion of the 1990 ACR criteria items for the classification of GCA

Original criteria	Suggested expansion
Age at disease onset ⩾50 years	Age at disease onset ⩾50 years
New onset headache of or new type of localized pain in the head	Any of the following: New onset headache of new type of localized pain in the head, **Visual symptoms, sight loss, PMR, Constitutional symptoms, Jaw and/or tongue claudication**
Abnormality of temporal artery (tenderness to palpation or decreased pulsation unrelated to arteriosclerosis)	Abnormality of temporal **and/or extra-cranial arteries** (tenderness to palpation or decreased pulsation, **bruits of extra-cranial arteries** unrelated to arteriosclerosis)
ESR ⩾50 mm/h	ESR ⩾50 mm/h and/or **CRP levels ⩾10 mg/l**
Abnormal artery biopsy	Abnormal artery biopsy and/or **abnormal imaging result (US, MRI and/or ^{18}F-FDG PET)**[a]

[a]Suggested new items are written in bold. These parameters are opinion based and should not be used in clinical practice or in clinical studies. A patient shall be said to have GCA if three of the five criteria are present, as long as either temporal artery biopsy and/or imaging results are compatible with a diagnosis of GCA. ^{18}F-FDG PET: 18-fluorine fluorodeoxyglucose PET/CT.

Time for an update of the 1990 GCA classification criteria?

Data from recent clinical, imaging and pathophysiological studies, and the recognition of GCA as a clinical syndrome that is not limited to cranial manifestations, lead us to consider whether it is time to expand the 1990 ACR classification criteria for GCA. The original study conducted by Hunder *et al.* to define these criteria was directed by the need to compare GCA with other vasculitides, and it was likely biased by the preferential recruitment of patients with cranial disease. Highly sensitive imaging techniques were not available at that time and extra-cranial arteritis was difficult to diagnose retrospectively unless ischaemic or aneurysmal complications occurred. The authors nevertheless included extra-cranial features of GCA such as PMR in an extended list of criteria [15].

In Table 2, we depict a proposal for how the 1990 ACR classification criteria for GCA could be expanded and made more relevant. We suggest that an abnormal temporal artery biopsy and/or appropriate imaging results compatible with GCA plus two out of the four other parameters be used to classify a patient as having GCA. We emphasize, however, that these parameters, at present,

are opinion based and should not be used in clinical practice or studies. These suggestions, we hope, will stimulate further data-driven efforts to update the classification criteria for a broader concept of GCA.

Conclusion

New data from imaging and pathophysiological studies indicate that GCA is a clinical syndrome with a range of manifestations from classic cranial GCA to LV-GCA and PMR. PMR may be a variant of GCA with a strong systemic inflammatory response, in which overt vasculitis has either not yet started or has been prevented by unclear regulatory mechanisms. Whether genetic factors (particularly the *HLA-DRB1**04 alleles as well as variants of cytokines, adhesion molecules and/or regulators of innate immunity) might determine the clinical phenotype needs to be investigated by future studies. There is also a need for histological, biomarker and/or animal model studies to evaluate the concept of a common pathophysiology of these conditions.

The 1990 ACR classification criteria for GCA focused on cranial manifestations, although the extended list of symptoms also includes PMR as a feature of GCA. Subclinical LV inflammation affects up to one-third of patients with PMR. Nevertheless, it is not current clinical practice to screen every patient with PMR for concomitant vasculitis. Patients with PMR who experience frequent relapses and constitutional symptoms should be re-evaluated for an alternative diagnosis (particularly GCA, other vasculitides and elderly onset inflammatory arthritis) and management plan.

Current treatment recommendations suggest using 12.5–25 mg/day and 40–60 mg/day prednisolone for initial treatment of PMR and GCA, respectively. Patients with LV-GCA as well as those with a phenotypic overlap between GCA and PMR should be treated with the same high-dose GC regimen as other GCA patients.

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