Polymyalgia Rheumatica and Giant Cell Arteritis

Third Edition

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Preface

In the present monograph, we offer current insights into polymyalgia rheumatica and giant cell arteritis. Both diseases are typical for advanced age, and their incidences increase with aging. Both diseases are a center point of interest not only for rheumatologists, gerontologists, ophthalmologists, or neurologists but also for general practitioners. Early diagnosis and rapid treatment, mainly with glucocorticoids, can save one of the most precious senses-vision. Damage to other organs (heart, aorta, coronary arteries, liver, lungs, kidneys), which are supplied by the arteries affected by ischemic syndrome in the setting of giant cell arteritis, has serious consequences as well. Late diagnosis of giant cell arteritis can have fatal consequences for affected patients. It is a matter of fact that the human population is aging. Therefore, more attention has to be paid not only to the diagnosis, clinical course, and treatment of rheumatic diseases in the elderly but also to their genetic, immunologic, endocrinologic, chronobiologic mechanisms and state-of-the-art diagnostic modalities. I am convinced that the interdisciplinary research of the diseases will allow us to diagnose and treat the rheumatic diseases even faster and more effectively in the future.

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1 Polymyalgia Rheumatica and Giant Cell Arteritis: An Overview with a Focus on Important Factors Contributing to the Severity of the Disease

Jozef Rovenský, Burkhard F. Leeb, Viera Štvrtinová, Richard Imrich, and Juraj Duda

1.1 Introduction

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) can be regarded quite rare systemic inflammatory diseases in the general population; however, their incidence increases with increasing age, and it may be anticipated that those disorders are frequently underrecognized. To diagnose both PMR and GCA, extensive clinical experience in rheumatology as well as in general internal medicine is mandatory. The most important prerequisite, though, is to consider the possibility of existing PMR or GCA in the respective patients. Although commonly considered typically for elderly patients (70 and above), the most recent surveys reported

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development of PMR and GCA also in the fourth and fifth decade. Moreover, also juvenile temporary arteritis and GCA have been reported in neonates and infants with fatal consequences [1, 2].

Although PMR and GCA are commonly regarded as two clinical variations of the same disease, their clinical picture is quite different [3, 4]. While in PMR the musculoskeletal symptoms predominate, arterial inflammation and its consequences constitute the major features of GCA, indicating higher clinical and pathological discrepancies between the two syndromes also with respect to morbidity and mortality [5].

1.2 Clinical Features

PMR and GCA are accompanied by several nonspecific symptoms, such as lethargy up to depression, fatigue, fever, loss of appetite and weight, and overall weakness. William Bruce described PMR symptoms for the first time in 1888 and named it "senile rheumatic gout" [6]. Usually, PMR shows an acute onset with severe and symmetric muscle pain in the shoulder girdle and the neck, less often in the pelvic girdle, accompanied by muscle tenderness without any swelling. Patients suffer from continuous pain often aggravated during physical inactivity or the night. However, sometimes the disease may be difficult to diagnose due to its slow and sluggishly progressing initial manifestations. Sometimes transient synovitis occurs without radiological signs of arthritis. Far too often, the symptoms are belittled to be primarily age related, even though with a simple erythrocyte sedimentation rate (ESR) testing, PMR could be easily taken into consideration. Given the correct diagnosis, the prognosis of PMR can be regarded excellent. Corticosteroids, the golden standard of all therapeutic measures, as a rule lead to a tremendous improvement of the affected patients.

GCA is a primary systemic vasculitis mainly affecting large vessels of the distal aortic arch. Clinical GCA findings depend on the location and scope of vessel impairment. Hutchinson gave the first clinical description of temporal arteritis in 1890 [2], and Horton et al. presented the histopathological findings in their relation to the clinical syndrome in 1932 [7]. Later, Gilmore [8] found that this form of vasculitis may also affect other arteries and introduced the term of "giant cell arteritis." Nowadays, GCA is clearly understood as a systemic disease with numerous severe and sometimes life-threatening cardiovascular complications. The variability and wide range of clinical findings and the clinical progression of the disease are presumably resulting from the heterogeneous immune and inflammatory response in the individual patient [9].

The leading clinical symptom of GCA is headache in two thirds of patients. Headache may be severe, sometimes radiating, most frequently located in the temporal area, sometimes in the occipital area, and experienced, e.g., on combing hair. The temporal arteries are thickened and tender, with palpable nodules along the artery and reduced or even absent pulsation. In any case of suspected temporal arteritis, an ultrasound examination, including the artery's temporal and masseter limb,

should be performed; the typical "halo" nearly proves the diagnosis [10]. Biopsy results depend on the length of the biopsy taken and the number of cuts investigated under the microscope [11], and GCA of the temporal artery does not necessarily constitute the only manifestation of the disease. Therefore, a negative biopsy result cannot be regarded as an absolutely excluding finding [12]. Recapitulatory, biopsy should be considered very important, as in doubtful cases, a biopsy of the temporal artery may contribute to an ultimate clarification; the required treatment, however, should not be postponed due to biopsy procedure.

1.3 Epidemiology

The annual PMR/GCA incidence is 1.7 to 7.7 per 100,000 inhabitants in elderly patients [13]. The incidence of PMR increases with the age of the population. PMR/GCA constitutes a relatively rare disease in people below 50 years, although it may also be present in younger adults [14, 15]. The younger a patient is, however, the lower the probability of PMR can be expected [16], and this likelihood decreases with male gender. The overall incidence in the general population totals to 20 to 50 new PMR cases per year per 100,000 people, with a fourfold higher risk for females to become affected [17]. There is evidence that the frequency of PMR cases may be somewhat dependent on the geographical region. In Europe, for example, the incidence rates are higher in the northern parts of the continent (e.g., Norway, 113 PMR cases per 100,000 inhabitants per year) in comparison to the southern parts (e.g., 13 per 100,000 per year in Italy) [18, 31]. In addition, the frequency of newly developed PMR cases shows fluctuations over time. That is why, relationships to infections, e.g., with *Chlamydia* or *Parvovirus* B19, or simply seasonal differences are in discussion [18, 19]. In 15 to 20% of PMR patients, the symptoms occur coexistent with biopsy-proven GCA, predominantly of the temporal artery. On the contrary, 40 to 60% of GCA patients have symptoms of PMR [16]. PMR is more frequent than GCA. As PMR patients without cranial symptoms are very unlikely to have positive findings on temporal biopsy, this procedure is only recommended in PMR patients with cranial symptoms, such as headache or jaw claudication [20], and a swelling which can be attributed to the temporal artery.

1.4 Laboratory Findings

Laboratory changes are generally nonspecific; as a hallmark, the acute phase response, measured by erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) or other parameters, is usually found highly elevated, even though PMR may also exist without elevated acute phase reactants [21]. Martinez-Taboada et al. [22] suggested a limit of 30 mm/h; however, Proven et al. [21] highlighted the fact that no difference in clinical findings and disease course in PMR and GCA patients with lower or higher ESR could be found, except for GCA with systemic changes, who had higher ESR values. Whether PMR with little or no elevation of acute phase

reactants can be regarded, a more benign disease is still in debate [21, 23]. Generally, mild microcytosis and thrombocytosis can be observed, while commonly the leucocyte count can be found within the normal range. Positive rheumatoid factor concentrations or elevated antinuclear antibodies are to be seen occasionally. Muscle enzymes, such as creatinine or aldolase, are in the normal ranges; sometimes, an elevation of the alkaline phosphatase can be observed. Liver biopsy performed in a group of PMR patients with increased alkaline phosphatase activity revealed mild portal and intralobar inflammation.

Malvall et al. [24] detected increased concentrations of IgG and C3 and C4 complement components in the serum of PMR patients. Recently, the presence of IgG anticardiolipin antibodies has been reported during GCA treatment, with a decrease during glucocorticoid treatment. In addition, an increase of sIL-2R concentrations was found in patients with active PMR/GCA with a decrease after 6 months of glucocorticoid treatment. Moreover, IL-6 levels were found elevated along with the increase of the sIL-2R concentration and an increase in the number of CD8+ lymphocytes. In patients with progressing or relapsing PMR/GCA, the number of CDS+ lymphocytes was found remarkably lower. Other authors reported increased factor VIII (von Willebrand) concentrations and increased IL-2 levels in some patients [25].

IL-6 levels were recently described not only as markers for disease activity assessment but also as prognostic markers but did not become part of the routine laboratory program yet, as its advantage over ESR or CRP is not that pronounced considering the costs [26]. All the other laboratory measures performed are rather targeted against potential differential diagnoses than to prove PMR [27, 28].

1.5 Differential Diagnosis

The more unspecific the patient's symptoms, the more important considerations become about eventually existing other disorders than PMR/GCA as the reason for the patient's complaints.

Myalgia may be a symptom of several diseases. Above all, late-onset rheumatoid arthritis (LORA) may start with widespread myalgic complaints [29]. However, arthritis, high titers of rheumatoid factors, and an only partial response to low-dose glucocorticoid treatment as well as involvement of the hand and finger joints allow some distinction between LORA and PMR [29]. Transient synovitis nevertheless may also be present in PMR patients, but PMR patients are expected to be typically rheumatoid factor negative. LORA (also called senile RA) typically begins as oligoarthritis with involvement of the shoulder joints. Overall manifestations of the disease are quite significant, while rheumatoid factors are often negative. Sometimes, the ultimate diagnosis can be clarified not earlier than after a certain period. Polymyalgic syndromes may also be of paraneoplastic nature [30]. The younger they are and the less impressive their response to corticoids is, particularly in males, the stronger a thorough examination of those patients can be given as a rough rule of thumb.

PMR-/GCA-like symptoms may also occur with hypothyroidism, with chronic infectious disorders and inflammatory myopathic disorder. Bilateral shoulder joint capsulitis can be quite easily distinguished from PMR based on passive movement limitations. Such examination may also be used to differentiate between PMR and osteoarthritis of shoulder and hip joints. Also, rotator cuff impingement syndrome can be differentiated by clinical examination (painful arc). Ultrasonography, revealing shoulder joint effusion, can be regarded significantly helpful with respect to differentiate between PMR and other disorders. In addition, an elevated acute phase response as measured by ESR and CRP and joint effusion as shown by sonography or MRI is hallmarked to diagnose PMR. GCA should be considered in every patient older than 50 with newly occurred headache, temporary or permanent loss of vision, myalgia, increased ESR, and fever of unknown origin. It should be emphasized that loss of vision may constitute the first manifestation of the disease, often without any prodromal symptoms. Visual disturbances have been reported more rarely in patients on corticosteroid treatment. Arteries of the head, the neck, and the extremities should be examined for tenderness or possible swelling or hypertrophy, they should be investigated for murmurs along their entire length, and peripheral pulsation shall be palpated on both upper extremities and lower extremities. To facilitate inclusion of patients into clinical trials, but also as an aid for daily routine, classification criteria have been developed. These criteria will be discussed in depth in the following chapters; however, the reader should always be aware that classifying a patient as suffering from a disorder does not mean the same as making a diagnosis [31, 32].

Involvement of large vessels in GCA patients may result in fatal consequences. Therefore, all patients suspected to suffer from GCA should be specifically examined for possible changes in these arteries. Blood pressure must be measured at both upper extremities; palpation for peripheral pulsation and auscultation for murmurs along large extremity vessels are highly recommended. The scope of vessel involvement can be examined using ultrasound and angiography, which may reveal smooth stenoses altered by slightly dilated sections or even occlusions. Moreover, typically bilateral localization and segmented involvement of the aorta and its branch can be visualized. Angiographic findings may guide interventions in patients not responding to conservative treatment. Doppler ultrasonography is a very useful and widely available method to confirm a first suspicion of vasculitis, but it has limitations especially at the large thoracic vessels, which are affected in many cases [10]. Laboratory markers alone are not sufficient to evaluate disease activity. The new imaging modality PET/CT provides the additional information. It allows the evaluation of disease activity and vessel morphology as well as the localization of the inflammatory process in the same session [33]. Temporal arteritis may be found also in case of other vasculitis disorders, such as Wegener's granulomatosis or microscopic polyarteritis. On the other hand, inflammation of the temporal artery not necessarily occurs in all GCA patients [34].

1.6 Etiopathogenesis

The etiology and pathogenesis of PMR and GCA are not elucidated yet. However, considerations in this respect are focused on environmental factors, particularly in infections with *Chlamydia*, *Mycoplasma*, parainfluenza virus or *Parvovirus* Bl9, and genetic ones. An association with the HLA system as well as several characteristic inflammatory reactions has been revealed. Cellular and humoral immune mechanisms are involved in the pathogenesis of both diseases. Some studies showed a reduction of CDS+ I-cells in both diseases. However, such a reduction has not been proven by other studies.

Increased levels of antiphospholipid antibodies have been detected in both PMR and GCA patients. However, clinical manifestations of an antiphospholipid syndrome have been rarely reported.

The occurrence of PMR/GCA in genetically predisposed patients may also be the consequence of many of neuroendocrine changes relating to natural aging.

Concentrations of several hormones are known to undergo changes in elderly, e.g., decrease in adrenal androgen levels such as of dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione (ASD). Reduction of adrenal androgen levels has been inversely correlated with concentrations of proinflammatory cytokines such as TNF and IL-6 [35]. Thus, the natural decrease of the adrenal androgens associated with an increase in the concentrations of proinflammatory cytokines at older age might predispose to the development of PMR and TA.

Analyses of adrenal hormones levels in patients with recent onset of PMR prior to the initiation of glucocorticoid therapy and their comparison with the levels in age and sex-matched healthy controls showed lower DHEAS concentrations in the PMR patients [36].

Another study showed lower baseline ASD levels in untreated male patients with PMR compared with healthy controls. However, in the latter study, no differences were found between basal DHEAS. Contrary to DHEAS, cortisol concentrations in patients at the time of the PMR diagnosis did however not significantly differ from those in healthy controls [37, 38]. An intricate feedback system probably maintains cortisol levels within the normal range. Because of the ongoing inflammation, however, cortisol secretion remains insufficient [38]. Also, a very good therapeutic response to the administration of exogenous glucocorticoids suggests that there might be a relative deficit of the endogenous hormones.

In another study, corticoliberin (CRH) and adrenocorticotropic hormone (ACTH) stimulation were used to evaluate the functional status of the hypothalamic-pituitary adrenal (HPA) axis in PMR prior to the initiation of the glucocorticoid therapy. No significant difference in the response of ACTH or cortisol was found when compared to healthy controls. However, similar ACTH response resulted in a higher secretion of 17-hydroxyprogesterone, which is a cortisol precursor, and ASD during [39]. In a study conducted by Pacheco et al., after low-dose ACTH challenge, higher responses of cortisol and DHEA were found in PMR patients than in control subjects [37]. Changes in steroidogenesis in terms of DHEAS reduction, relative

cortisol deficit accompanied by the accumulation of the precursor of the latter, could represent additional factors of the pathogenesis of PMR and GCA.

The ultimate reason for the outbreak of PMR and GCA development has not been revealed yet. It may be somewhat like viral disease. A possible relation between hepatitis B and PMR has been considered. Some studies revealed seasonal variations with respect to the onset of the disease. Mowat and Hazleman [5] stated that more PMR cases occurred in winter and summer months and less in spring and autumn. Perfetto et al. [40] consider two possible synergic mechanisms possibly involved in a season depending onset of PMR; first they found PMR/GCA peaks closely related to the epidemic peak occurrence of mycoplasma pneumoniae and parvovirus Bl9 infections. Second, seasonal changes in the immune system make human organism more responsive to the development of various diseases including PMR.

As in rheumatoid arthritis, the HLA DRBl*04 and DRBl*01 alleles are linked to an increased susceptibility to both PMR and GCA and may also have an impact on the severity of the disease [41]. Antigen recognition by T cells in the adventitia with subsequent production of interferon-y and activation of macrophages as well as formation of giant cells could constitute the key process for the development of GCA. Those activated macrophages produce proinflammatory cytokines such as TNF-a, IL-1, and IL-6 in the adventitia, while in the intima and media, they lead to injury by producing metalloproteinases and nitric oxide. The destructive process initiated thereby and the simultaneous repair mechanisms lead ultimately to the occlusive luminal hyperplasia.

IL-6 production was found increased in serum as well as in temporal artery biopsies of PMR and GCA patients as well as a potential role of the promoter polymorphisms of IL-6 for the clinical expression of PMR and GCA [41].

1.7 Ophthalmologic Manifestations in GCA Patients

50% of patients were affected by significant changes in vision due to the occlusion of ocular arteries and orbital arteries. Anterior ischemic optic neuropathy is often reported in GCA patients and can be regarded the primary reason for loss of vision. In the last 30 years, its occurrence significantly decreased due to the advances in diagnosing GCA. Nevertheless, still up to 15% of the patients develop this complication. Ischemia of the anterior optic nerve is mainly reported because of the involvement of the posterior ciliary artery, a branch of the ophthalmic artery supplying the optic nerve's papilla. Autopsy-proven vasculitis of the posterior ciliary artery has been reported in 75% of GCA patients, usually without clinical manifestations.

Acute visual impairment often developing overnight in the form of blurred vision, diplopia, light scotomas, visual field narrowing, or even transient or irreversible blindness (reported in less than 10% of patients) has also been reported. In more advanced cases, atrophy of the optic nerve's papilla may develop. In some cases, retrobulbar neuritis without any ophthalmologically noticeable changes of the optic

nerve or segmental ischemia of the optic nerve papilla due to segmental optic neuritis has been described. In such cases, GCA affects the posterior ciliary artery or nutritive optic nerves. Rarely loss of vision occurs also due to an occlusion of the central artery of the retina or due to retinopathy with hemorrhage. Visual impairment primarily affects one eye; however, if untreated, it may turn to two-sided blindness. The occurrence of diplopia due to the involvement of the oculomotor, abducens, or trochlear nerves is quite rare and has been reported only in 2% of GCA patients. Visual disturbances in any instance constitute an emergency, necessitating immediate physician's action, as primarily early recognition of visual disturbances alerting potential vision impairment (temporary scotomata, phosphorescent phenomenon, etc.) can contribute to prevent vision loss [12, 42–47].

Some improvement in diagnostics may be expected thanks to the use of imaging techniques, such as colored Doppler sonography of optic vessels or fluorescent angiography enabling to determine the scope of the optic vessel impairment.

1.8 Neurovascular Manifestations in GCA Patients

GCA may affect the central nervous system (CNS), cranial nerves, as well as peripheral nerve system. Neurological manifestations have been reported in approx. 20–30% of the patients, caused by vasculitis of nutrition vessels. Clinical manifestations may comprise deafness, hemiparesis, depression, confusion, and peripheral neuropathy (in approx. 10–15% of patients) due to mononeuropathy and peripheral polyneuropathies, which are often diagnosed before the GCA diagnosis is established. Bilateral neuropathy due to GCA mainly affecting the median nerve has been reported in up to 40% of patients. The brachial plexus may also be involved making it difficult to distinguish the disease from the oppression of C5–C6 root. Glucocorticoid treatment has been reported successful in 74% of patients, while in the other 26% of the patients, no deterioration had to be noticed [48].

Aside from pain in the temporal and/or occipital area, pain in the masseter muscle (masseter claudication) has been reported in 50% of patients. GCA manifestations may also include stitching pain in the tongue, loss of appetite, and pain felt in mouth and pharynx due to vascular insufficiency.

Cerebrovascular impairment, presenting as strokes or transitory ischemic attacks (TIAs), is only rarely observed in GCA patients; per Nesher in 166 biopsyproven GCA patients, ten experienced a TIA and five a stroke [48]. It should also be mentioned that cerebral vascular accidents (CVA) have been reported primarily in elderly patients and may be caused not by GCA but by simultaneously progressing arteriosclerosis. Vertebrobasilar ischemia occurs more often in GCA patients (40–60%) than in patients with arteriosclerosis (15–20%). Nevertheless, CVA represents one of the main reasons for they may become fatal in case of undiagnosed GCA and late GCA diagnosis.

Ischemic accidents have been reported to occur more frequently in patients with visual disturbances and in patients with jaw claudication. It can be assumed that simultaneous application of thrombocyte-aggregation inhibitors or anticoagulants

may reduce the risk for an early stroke [49], as GCA probably accelerates atherosclerotic changes [50].

Neuropsychiatry manifestations in GCA patients include disorientation, dementia, impairment of cognitive and memory functions, mood changes (depression), and psychoses. Visual hallucinations have also been reported in patients with vision impairment or loss. It should also be mentioned that GCA might constitute the basis for the development of dementia. In these patients, glucocorticoid treatment may improve the patient's condition.

Audiovestibular manifestations have been reported in 7% of patients in the form of monolateral or bilateral deafness, vertigo, or tinnitus with a beneficial effect of glucocorticoid treatment.

1.9 Involvement of the Upper and Lower Extremities in GCA Patients

GCA rarely affects the arteries of the upper and lower extremities. In those cases, vessels distal to the subclavian and brachial artery and the femoral superficial as well as the popliteal artery are involved. Claudication constitutes the leading clinical symptom.

Up to now, only a few patients with histologically proven GCA in the lower extremities (LEs) have been reported. Garcia Vazques et al. [51] report a 52-year-old patient with ischemia in upper and lower extremities, more pronounced in the left leg, suffering from ischemic pain for 6 months without any risk factors for arteriosclerosis, such as smoking, hypertension, increased cholesterol and triglyceride levels, or diabetes mellitus. Ischemic disorder of the left leg worsened up to the level III disorder, including bilateral loss of pulsation. The temporal artery was palpable, but not painful. The patient had a high sedimentation rate (112 mm/h) and increased serum values for albumin. Angiography revealed stenosis in both subclavian arteries (30% on the right, 70% on the left side) as well as a filiform stenosis of the left superficial femoral artery and stenosis of a lower degree of the right one. GCA diagnosis has been proven by positive biopsy from both the temporal and the superficial femoral arteries. Sympathectomy was unsuccessfully performed at both sides, while glucocorticoid treatment, 40 mg daily dose gradually reduced to 10 mg a day, was of transient efficacy. After 3 months, the patient relapsed, and the corticosteroid dosage had to be re-increased to 30 mg a day. After 2 years, angiographic reexamination showed significant improvement regardless of some segmental narrowing of the left femoral superficial artery and development of large collateral connections.

In 1997, Dupuy et al. (SO) reported two patients with GCA of the lower extremities with an initial reduction of the walking distance down to 30 m [52]. The first patient was a 61-year-old woman with hypertension and without any signs of arteritis of the external carotid artery and its branches. She had a high sedimentation rate (exceeding 100 mm/h) and C-reactive protein values (21 mg/l). Temporal biopsy was negative. She was put on nonsteroidal antirheumatic and antimalarial

treatment, while pain in the right foot progressed and the patient was not able to walk for more than 30 m. The ultrasound examination showed numerous stenoses in the femoral artery and its distal branches (right superficial femoral artery, popliteal and sural artery, left superficial femoral artery). Biopsy of the right superficial femoral artery showed arteritis with giant cell granulomatosis proving GCA diagnosis. Prednisone treatment (1 mg/kg body weight) and hydroxychloroquine treatment (400 mg) were successful. After 1 month of treatment, pain had disappeared and the walking distance could be increased. After 6 months of treatment, the patient could easily walk 3 km, and pulsation of the dorsal pedis artery reoccurred. Despite of a partially narrowed superficial femoral artery, the angiographic examination showed satisfactory calibration of both tibial arteries. After a 2-year treatment, the patient received 5 mg prednisone/day and felt no walking limitations [52].

The second patient was a 65-year-old woman, suffering also from Parkinson's disease with severe depression treated with levodopa, bromocriptine, and tricyclic antidepressants. During 1 month, claudication of the lower extremities gradually worsened. The patient was also subject to dihydroergotamine treatment for persistent migraine. Despite of this treatment, headache was worsening above both temporal arteries developed. The patient's sedimentation rate reached 80 mm/h. Diagnosis of toxic dihydroergotamine effects could not be proven. Therefore, diagnostic efforts were undertaken to prove the evidence for arteritis. Ultrasound examination showed a narrowed lumen of the superficial femoral and popliteal artery on both sides; angiography revealed bilateral narrowing of the iliac, femoral, and infrapopliteal arteries. Temporal artery biopsy suggested the presence of GCA as it showed clusters of lymphocyte infiltrates spread over the entire artery wall and fragmentation of the internal elastic lamina. There were neither any giant cells nor eosinophilic cells in the periadventitia. After prednisone treatment for 2 months (1 mg/kg/day) in combination with anticoagulants, the patient's headache disappeared, and she could easily walk without any pain for a longer distance. After 1 year of treatment, the ESR and CRP were normal, but pulsation of the arteria dorsalis pedis did not reoccur [52].

Claire Le Hello et al. [53] described eight GCA patients (six females, two males), all suffering from lower extremity claudication with acute onset. In six cases, claudication represented the primary disease symptom. Angiographies revealed numerous bilateral flat-walled stenoses and thromboses. Five patients met three of the American College of Rheumatology (ACR) criteria for the diagnosis of GCA. Biopsies of the affected arteries revealed GCA in four patients. In one patient, the CGA diagnosis was proven postmortem. In three patients, GCA could not be proven histologically from biopsy of arteries of the lower extremities. However, in one of them, temporal GCA could be proven. Two other patients suffered from headache and upper extremity claudication as well as angiographic signs of arteritis in the lower limbs. All the patients were subject to glucocorticoid treatment; four of them underwent vascular surgery (three bypasses and one endarterectomy). Five patients were asymptomatic after 24–100 months (50.6 months in average). Surgical revascularization appeared to be unsuccessful; in one patient, it was even necessary to amputate the patient's extremity.

In summary, the authors concluded that in case of acute onset of bilateral, fast progressing claudication with partial or complete loss of peripheral pulsation GCA should be considered. The necessity to consider GCA in cases of all unexplained peripheral arterial obliterating diseases in middle-aged and elderly patients, given the possible consequences of vascular impairment, was also emphasized. The authors also refer to autopsy findings indicating that GCA, contrasting previous assumptions, cannot be considered a rare disease [54]. Thus, biopsies of the lower limb arteries in case of unclear symptomatology are recommended. Peripheral arterial obliterating disease of lower extremities may not only be caused by arteriosclerosis but also by vasculitides, such as GCA. Laboratory findings indicating inflammation should constitute an alert for the evidence of GCA. Delayed initiation of steroid treatment may result in severe consequences for the patient including the loss of an extremity.

1.10 Other Clinical Manifestations

GCA as an aggressive inflammatory disease may affect arteries in all parts of the human body. Coronary arteritis may result in myocardial infarction and congestive heart failure; dissecting aortic aneurysm may result in aortic rupture [54]. GCA rarely affects the skin, kidneys, and lungs. High sedimentation rate and CRP values can be regarded specifically relevant to consider GCA.

Case reports describing two GCA patients from eastern Slovakia also deal with the difficulties to diagnose GCA [55]. The first patient was a 77-year-old woman suffering from seronegative rheumatoid arthritis since 1975. Patient's history revealed pain in the shoulder and pelvic girdle, long-lasting morning stiffness, weight loss, increasing headache, and one episode of acute vision loss in 1987. At that time, the ESR amounted to 90 mm/h. The patient was treated in an ophthalmologic unit. One year later, she was examined by a rheumatologist, and biopsy proved temporal arteritis. Prednisone treatment (50 mg/day) was reduced at a surgical department where partial amputation of the left lower limb was performed. Histological examination proved GCA of the tibial artery. The patient died after the last amputation due to pulmonary embolism.

The second patient was an 83-year-old woman treated at a dermatological unit due to lupus erythematosus since 1967. In 1986, the patient was for the first time examined by a rheumatologist for visual disturbances. At that time, PMR with GCA and significant bilateral amaurosis was diagnosed. Clinical findings mainly comprised pain, stiffness, and atrophy of the pectoral girdle muscles. The patient received glucocorticoids for a short time, which was interrupted for diarrhea, abdominal pain, and tenesmus. The patient's condition worsened progressively, and she died within a short time. Autopsy revealed bilateral GCA of the temporal artery and arteritis of the renal and mesenteric arteries.

Both cases can be summarized as late diagnosed GCA, involving the temporal as well as other arteries, with insufficient glucocorticoid treatment and fatal outcomes [55].

1.11 Prognosis of GCA and Temporal Arteritis

GCA is a systemic granulomatous vasculitis of unknown etiology typically affecting the branches of carotid artery (particularly the temporal artery), but it also may affect any medium-sized or large artery. The recognition of involvement of other than cranial arteries is considered more difficult [56].

GCA in general does not significantly reduce life expectancy of the patients, if it is early diagnosed and accordingly treated [56]. Save-Soderbergh et al. [13] describe the causes of death of nine GCA patients: two of them died due to myocardial infarction, another two patients due to dissecting aneurysm, and five due to sudden cerebral vascular accident. None of these patients had been treated with corticosteroids adequately. Lie [57] analyzed 18 patients with extracranial GCA and found aortic aneurysm rupture as the cause of death of 6 patients, another 6 patients died due to aortic dissection, 3 patients due to sudden cerebral vascular accident, and another 3 patients due to myocardial infarction. We have described two patients with GCA-causing fatal aortic aneurysm dissection [55].

Temporal arteritis per se (i.e., the arteritis affecting temporal artery) cannot be regarded a life-shortening disease. There is no difference regarding life expectancy between affected patients and the non-affected population; however, GCA affecting large- and medium-sized vessels may develop life-threatening consequences, such as aortic dissection or rupture, in myocardial infarction or cerebral vascular accident [58].

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Polymyalgia Rheumatica, Temporal Arteritis, and Occurrence of Malignant Tumors

2

Jozef Rovenský and Alena Tuchyňová

Polymyalgia rheumatica (PMR) and temporal arteritis (TA) are clinical syndromes characterized by their onset at advanced age. Little is known about the etiopathogenesis of these two nosological conditions. TA has recently been suggested to be an autoimmune syndrome that results from the immune response of the body against antigens localized in the walls of certain vessels [1]. Peptides of elastin are considered to be among the presumed targets of the autoimmune reaction [2].

The clinical picture of these syndromes is variable and thus their diagnosis is rather difficult. This is also due to a lack of specific diagnostic tests, in particular to PMR. Differential diagnosis of PMR or TA requires an exclusion of several other diseases with similar symptomatology. These include primarily infections and tumors, which are more common in elderly and are frequently manifested as polymyalgia-like syndrome. Naschitz et al. [3] studied the incidence of cancer in 47 patients with PMR over a period of 10 years. In five of these patients, polymyalgia-like syndrome was discovered 1–3 months before malignancy was diagnosed. In all these patients, scintigraphic examination detected metastases localized in bones and joints, while the primary tumor was in the lungs (1 patient), kidneys (1 patient), and colon (2 patients), and in one patient the localization of the primary tumor could not be established. An interesting observation in this series was the atypical course of the polymyalgic syndrome, which differed from classical PMR by the onset of complaints before the age of 50 years, by affecting only one typical site, asymmetrically affecting an

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typical localizations, by pain in the joints and by partial or delayed effect of prednisone on the relief of symptoms. The authors assumed that patients with an atypical course of PMR are at a higher risk of developing a malignancy metastasizing into bones of articulations.

On the other hand, cases of PMR and/or TA coexistence with tumor diseases have also been reported. The interval between the manifestation of PMR and TA and diagnosis of malignancy was sufficiently long for the polymyalgic syndrome not to be considered a paraneoplastic one. As early as in 1969, Mackenzie [4] described the development of malignancy in one subject of a series of 76 patients with PMR. Several papers have appeared since addressing the potential association between PMR and/or TA and the incidence of malignant tumors (Table 2.1). Probably the most detailed study was published by Haga et al. [5] who investigated the incidence of tumor diseases in 185 patients with PMR and/or TA in a prospective study covering the years 1978–1983. A series of 925 subjects randomly selected from the Central Population Registry of Norway served as controls. The data obtained from the patients and from the control subjects were compared with data from the Cancer Registry of Norway. By the end of the 5-year study, malignancy was found in 27 patients (14.6%) with PMR and/or TA and in 131 subjects (14.2%) from the control group. A higher occurrence rate of malignant tumor diseases was recorded in 16 patients with histologically verified TA (24.6%). In this subgroup of patients, the risk of developing malignancy was 2.25 times higher than in the control group and 4.4 times higher compared to the other patients with PMR and TA. In 13 patients of the series, the malignancy preceded PMR and/or TA diagnosis by 4–17 years. In 14 patients of the series, PMR and TA were manifested first, and malignancy was diagnosed in the course of 3 months up to 7 years. In the light of the relatively long interval between the diagnosis of malignancy and PMR and/or TA, the authors do not consider the manifestations as a paraneoplastic syndrome.

It appears that the number of studies has been growing, in which authors reported the occurrence of PMR, TA, and malignancies, though the majority of them were case reports. The primary localization of the malignant tumor covered a broad range. Haga et al. [5] reported predominantly tumors localized to organs, yet other authors published findings on the occurrence of leukemia [6, 11, 16], non-Hodgkin's lymphoma [7], or Waldenstrom's macroglobulinemia [6, 12]. In our series of 26 patients (18 patients with PMR, 8 patients with TA), we did not observe any malignancies either before diagnosis of PMR or TA was established or in the course of the 3-year prospective follow-up of the patients. These results are to be considered preliminary, especially with regard to the short follow-up interval from setting up the diagnosis and from the onset of treatment. We did, however, perform a research probe in a retrospective study of the clinical material of 42 patients with PMR or TA, who had been hospitalized in our institute after 1972. Association with malignancy was detected in two patients. One of them underwent hysterectomy for rhabdomyosarcoma 9 years before PMR was diagnosed, and in the second patient, breast cancer was detected 1 year before the appearance of PMR. Malignancy was not found in any of the patients with TA.

Table 2.1 Survey of published papers about the incidence of malignant tumors in patients with PMR and TA

Author (ref.)	No. of patients	Diagnosis	No. of patients with malignancy	Localization/type of tumor (s)
Kalra and Delamere [6]	Case reports	PMR	5	Monoclonal gammopathy acute myeloblastic leukemia, multiple myeloma, susp. Waldenstrom's macroglobulinemia
Montanaro and Bizzarri [7]	Case report	PMR-like syndrome	1	Non-Hodgkins lymphoma later transformed into acute lymphoblastic leukemia
Haga et al. [5]	185	PMR and/or TA	28	Carcinoma uteri (3), recti (5), renis (2), pancreatis (1), ovaries (1), vulvae (1), penis (1), mammae (3), ventriculi (1), testis (1), prostate (1), coli (5), lungs (1), lymphonodorum (2)[a]
O'Keefe and Goldstraw [8]	Case report	PMR	1	Non-small cell carcinoma of lungs
Tabata and Kobayashi [9]	Case report	PMR	1	Papillary carcinoma of the thyroid gland
Kohli and Bennett [10]	Case reports	PMR	3	Myelodysplastic syndrome
Shimamoto et al. [11]	Case report	TA	1	Acute myelogenous leukemia
Mertens et al. [12]	111	PMR and/or TA	12	Breast (1), skin (2), colon (2), stomach (2), hypernephroma (2), ovaries (1), lungs (1), Waldenstrom's macroglobulinemia (1)
Lie [13]	Case report	TA	1	Adenocarcinoma of lungs
Das-gupta et al. [14]	Case report	PMR	1	IgA kappa paraproteinemia
Genereau et al. [15]	Case report	PMR	1	Urinary bladder
Gonzáles-Gay et al. [16]	Case report	TA	1	Chronic lymphocytic leukemia
Assi et al. [17]	Case report	TA	1	Squamous dermatocarcinoma
Bahlas et al. [18]	149	PMR and/or TA	4	Multiple myeloma (2), squamous cell carcinoma, carcinoid, lymphoma (3)
Liozon et al. [20]	271	TA	20	Thyroid, rectum, prostate, sigmoid colon, mediastinum, bladder, gastric, neuroendocrine, uterus, gastric, brain (astrocytoma), B cell chronic lymphocytic leukemia, refractory anemia, chronic myelomonocytic leukemia, acquired sideroblastic idiopathic anemia, chronic myelogenous leukemia

[a]In one patient several primary localizations of the malignant tumor

Pipitone et al. concluded that there is no evidence that giant cell arteritis is associated with increased prevalence of malignancies or that it may represent a paraneoplastic syndrome [19].

On the other hand, Liozon et al. [20] found that concurrent malignancy in TA is not a rare finding, observed in up to 7.4% of the cases. Solid malignancies and hematological disorders, especially myelodysplastic syndromes, may represent precipitating factors for development of TA, which are often of paraneoplastic origin. Patients with and without malignancy seem to be almost indistinguishable in terms of features and outcome of TA. Physicians should be aware of this potential association, even in typical cases.

Nevertheless, despite the abovementioned findings, patients with giant cell arteritis and also patients with PMR may be considered at risk of developing malignancy. This assumption is supported by several factors: the higher occurrence rate of tumor diseases in subjects of advanced age, presumed derangement of some functions of the immune system in patients with TA and PMR, known coincidence of malignancies with dermatopolymyositis and vasculitis, and alterations in the immune response brought on by therapy administered. To confirm the given assumption, prospective studies need to be performed on larger series of patients. Due to the low number of patients with TA and PMR, the problem will have to be investigated in terms of international cooperation using adequate mathematical and statistical methods in evaluating the obtained results.

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Polymyalgia Rheumatica, Giant Cell Arteritis, and Vascular Complications

3

Viera Štvrtinová, Denisa Čelovská, Svetoslav Štvrtina, and Jozef Rovenský

3.1 Polymyalgia Rheumatica

Polymyalgia rheumatica (PMR), similarly as other rheumatic disorders, may be linked to an increased risk of vascular diseases [1]. PMR may be associated with vascular complications for a number of reasons: (1) the inflammatory nature of the disease itself, (2) strong association with giant cell arteritis (GCA-which has a direct inflammatory effect on arteries and may result in either stenosis or aneurysm within the affected segments), and (3) side effect of the corticosteroid treatment (including arterial hypertension, dyslipidemia, and/or diabetes mellitus). Paradoxically, on the other hand, corticosteroids in patients with PMR may decrease vascular risk by controlling inflammation [2].

Some studies reported a statistically significant positive association between PMR and vascular mortality [3, 4] while others did not. Schaufelberger et al. reported an increased all-cause mortality rate among a group of 220 patients with PMR. They observed 41 deaths in their cohort, compared to 29 expected deaths [3]. A Swedish team also reported increased standardized mortality rates for vascular diseases among patients with PMR and GCA [4]. A team from Minnesota reported

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statistically significant associations between PMR and various vascular complications, e.g., an increased risk of peripheral arterial disease (PAD) in a group of 353 patients with PMR [5].

PMR is a syndrome closely associated with giant cell arteritis (GCA), and it is often considered a single disease [6]. Approximately 40–50% of patients with GCA have symptoms of PMR, before, at the same time, or after the diagnosis of GCA [7]. Symptoms of PMR include morning stiffness and proximal muscle pain especially in the neck, shoulders, and in the pelvis. The muscle pain is symmetric; muscles are pressure sensitive without edema [8]. The main complaints of PMR patients are morning stiffness with inability to stand up from the supine to the upright position and inability to comb hair. In cases of vasculitis affecting temporal artery and its branches, the pain is usually provoked by hairbrush contact with the inflamed artery wall. It is evident that if PMR is associated with vascular complications, then GCA, which causes greater level of inflammation and thus requires higher dosage of corticosteroids, would have a stronger association with vascular diseases than PMR.

3.2 Giant Cell Arteritis

GCA is a systemic granulomatous vasculitis of unknown etiology, typically affecting branches of the carotid artery, mainly the temporal artery; however, any other medium or large artery can be affected. This fact complicates diagnosis of the disease.

Temporal arteritis is the most common form of GCA. In the tenth century, Ali Ibn Isa, an Arab ophthalmologist, recommended temporal artery excision in patients with migraines, who also had chronic eye disease progressing to vision loss [9]. Clinically, Hutchinson described temporal arteritis for the first time in 1890. Histopathological findings were correlated with the clinical syndrome by Horton in 1932. Only in 1938, Jenning recognized the loss of vision as a disease complication. A few years later pathologist Gilmore found that temporal arteritis can affect any other artery and named the disease "giant cell arteritis" [10].

Nowadays, it is clear that GCA is a systemic disease with several serious, life-threatening cardiovascular complications. A diverse clinical presentation and a course of the disease are due to heterogeneous immune and inflammatory reactions [11]. GCA most often affects branches of the carotid artery; however, granulomatous panarteritis can be found in any other medium or large-size artery. The term "temporal" is often used in quotes since it describes probable but not inevitable inflammation of the temporal artery in GCA. The temporal artery can be affected in other diseases such as Wegener's granulomatosis or microscopic polyarteritis. On the other hand, the temporal artery is not necessarily affected in all patients with GCA [12]. Temporal arteritis, i.e., arteritis affecting the temporal artery is not a deadly disease; patients' life expectancy is comparable to that of the general population. GCA of large arteries can be, however, a lethal disease presented by a dissection or rupture of aorta in the elderly [13, 14], as well as by a myocardial infarction or stroke [15]. GCA is the most common chronic systemic vasculitis affecting people aged over 50 years [16]. Very rarely, a juvenile form of the disease is confirmed by histological investigation [17, 18].

3.2.1 Incidence

In 1981, in Goteborg, Sweden, incidence of histologically confirmed GCA was found to be 5.5 cases per 100,000 subjects or 16.8 cases of persons older than 50 years per 100,000 subjects [19]. In Minnesota, USA, an average incidence of the disease increased from 5.1 per 100,000 in the 1950s to 17.4 per 100,000 in the early 1970s [20]. The increased incidence of GCA can be due to improved diagnostic of the disease. The GCA incidence of 2.2 per 10,000 was found in the Great Britain in the years 1990–2001. PMR incidence was found to be even higher, 8.4 cases per 10,000 [21]; both diseases often occurred in summer and were more frequent in southern parts of the country.

The number of incident cases of GCA will increase secondary to the aging population. Between 1980 and 2004, the mean age at diagnosis of GCA for people in the USA was found to be approximately 75 years of age [22], and mean life expectancy is predicted to be approximately 83.8 years by 2050 [23]. By 2050, more than 3 million people will have been diagnosed with GCA, in Europe, North America, and Oceania. Approximately 500,000 people will be visually impaired. By 2050, in the USA alone, the estimated cost from visual impairment due to GCA will exceed 76 billion US dollars. Management of steroid-related adverse events will increase costs further, with steroid-induced fractures estimated to total 6 billion US dollars by 2050 [24].

GCA is a disease often found in the Caucasian population; it is relatively rare in other ethnic groups. The disease is twice more frequent in women than in men. The inflammation associated with the disease is more severe in women, and the period of treatment is longer than in men [25]. The majority of data on GCA and PMR are from studies in the Northern Europe and the North America.

3.2.2 Etiology

The etiology of the disease is unknown; however, a genetic predisposition and autoimmune mechanisms are often considered in the disease pathogenesis. Predominant occurrence in the Caucasian population, family history, and an association with HLA-DR4 antigen is supportive of its genetic etiology [9, 26].

Immune cell mechanisms and deposition of immune complexes play an important role in the GCA pathogenesis. Increased concentrations of IgG, IgA, and IgM were found in subjects with GCA. Antibody and complement deposits were confirmed by immunofluorescence in the affected arteries. Macrophages, epithelial-like cells, and giant cells in arterial lesions produce various adhesion molecules such as ICAM-1. These findings suggest that inflammatory reaction in GCA depends on T cells reacting with antigens presented by tissue macrophages. Increased production of IL-1 beta and IFN-gamma appears to be an important factor modulating hyperplasia of intima in the affected blood vessels. Systemic concentrations of IL-6 are increased in GCA, whereas glucocorticoid therapy decreases IL-6 levels [27]. Activation of blood mononuclear cells represents an additional mechanism to arteritis itself [28]. Hypothyroidism with the presence of thyroid-specific antibodies was found in 10% of subjects with GCA [27].

The sudden onset of the disease and geographical differences in GCA and PMR incidence suggest that environmental factors play an important role in the disease pathogenesis. Olsson and coworkers [29] found an increased prevalence of GCA and PMR during two epidemics caused by *Mycoplasma pneumoniae*. The seasonal occurrence of PMR and GCA has been associated with epidemics of *Chlamydia pneumoniae* and parvovirus B19 [30]. Other possible mechanisms include seasonal changes of immune function causing variations in susceptibility to some diseases [25]. Neuroendocrine mechanisms associated with aging can play a role in genetically predisposed individuals. Analysis of these changes is complicated by complex feedback relationships between inflammation and the neuroendocrine system. Good therapeutic response of glucocorticoids supports relative decrease in cortisol in PMR and GCA patients.

3.2.3 Histopathology

One of the typical findings in GCA is a granuloma, i.e., focal inflammation in the media of the affected blood vessels, as seen in the case of an 86 years old man (Fig. 3.1). Elastic fiber structures disappear in the granuloma. Another typical histologic finding for GCA is a multinucleated giant cell (Figs. 3.2 and 3.3).

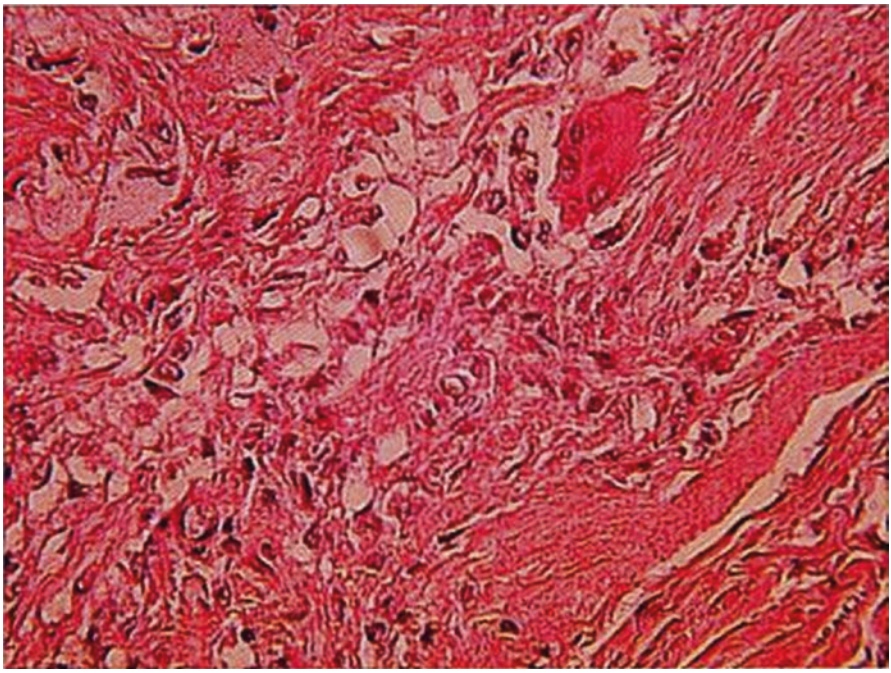

Fig. 3.1 Granulomatous inflammation of the media of abdominal aorta. Stained with HE—hematoxylin-eosin. Inflammatory infiltration formed mainly by histiocytes and plasmatic cells, less from lymphocytes, multinucleated giant cell

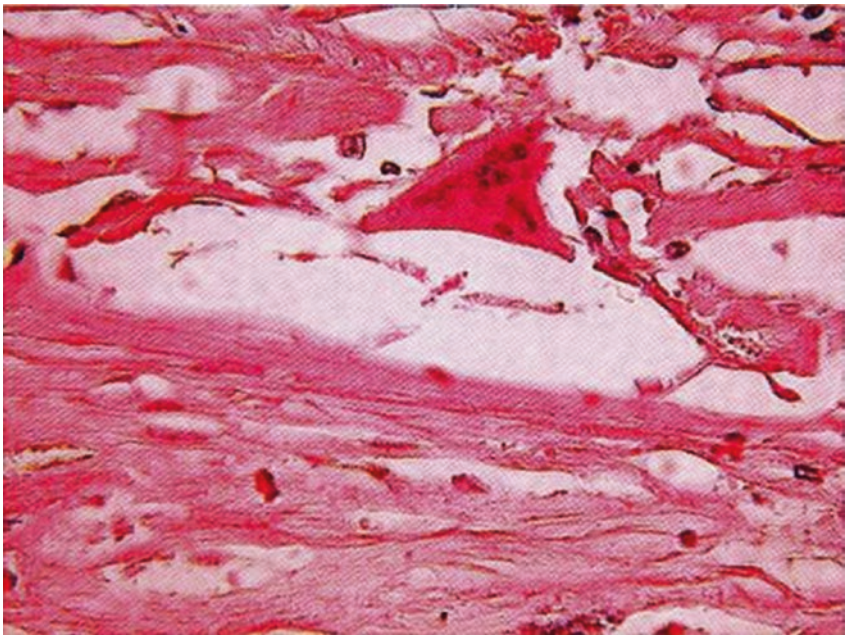

Fig. 3.2 Multinucleated giant cell. Stained with HE

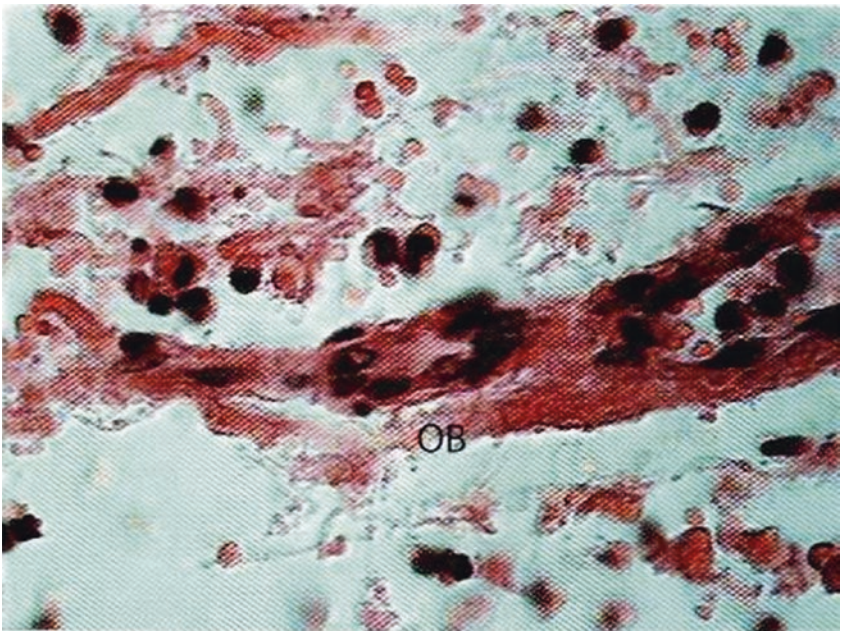

Fig. 3.3 Aortic wall—mixed inflammatory infiltrate, histiocytes, and giant cell (*OB*) in adventitia. Stained with HE

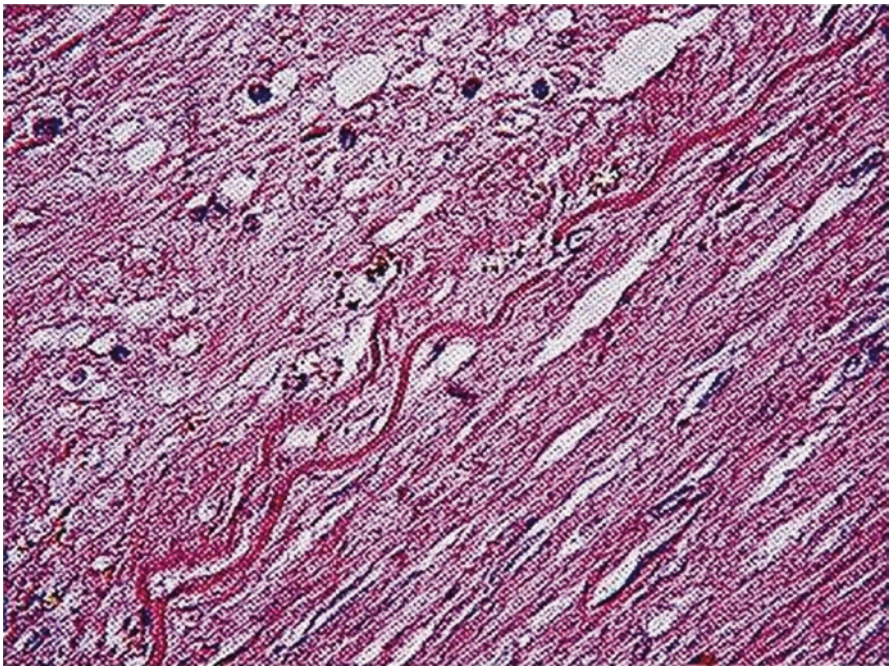

Fig. 3.4 Dissection and fragmentation of the internal elastic membrane. Stained with HE

All vascular layers, the media in particular, are affected in GCA. Splitting and fragmentation of the inner elastic membrane is typical of GCA (Fig. 3.4). Focal inflammation consisting of giant cells affects blood vessel walls showing signs of smooth muscle atrophy and calcification in media.

Typical deposits of calcium salts can be seen in the internal elastic lamina of the aorta in a biopsy in an 84-year-old woman (Fig. 3.5). Calcium deposition in the internal elastic lamina is a typical finding in GCA. Giant cells destroy the inner elastic membrane and incorporate calcified parts of the membrane. Apparently, calcified parts of the internal elastic lamina and atrophy of the media lead to inflammatory reactions [31]. Calcifications of the inner elastic membrane are morphologically different from those in Monckeberg's medial sclerosis, as well as from those in atherosclerosis, which are located in intima [32] (Fig. 3.6). Perhaps, these morphological differences cause accumulation of giant cells around calcifications in the internal elastic lamina. Analysis of vascular segments not affected by inflammatory reaction showed more severe smooth muscle atrophy and calcifications of the internal elastic lamina in GCA compared to healthy persons. The arteritis can be a result of metabolic changes in the arterial wall, which leads to atrophy of smooth muscles in the media and to degeneration and calcification dystrophy of the inner elastic membrane [31].

Giant cells present antigens for T cells, which subsequently produce cytokines. These cytokines attract macrophages, responsible for tissue damage in the affected artery by a production of reactive oxygen and nitrogen species and matrix metalloproteinases. The fragmentation of the internal elastic lamina facilitates migration of

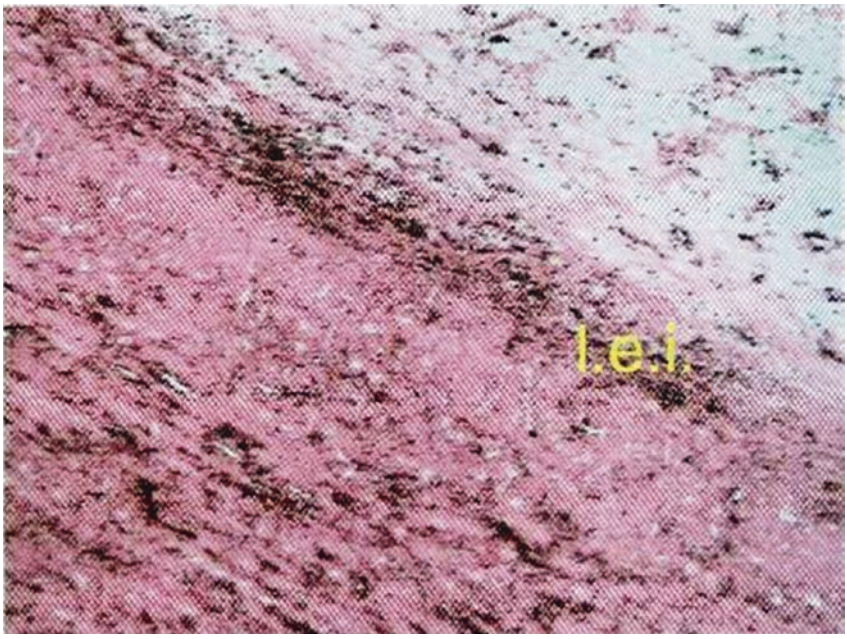

Fig. 3.5 Typical calcium powder in the internal elastic lamina (l.e.i). Stained with Kossa and HE

Fig. 3.6 Calcium deposits (*1*) in the internal elastic lamina, sclerotic plaque with calcium in intima (*2*). Stained with Kossa and HE

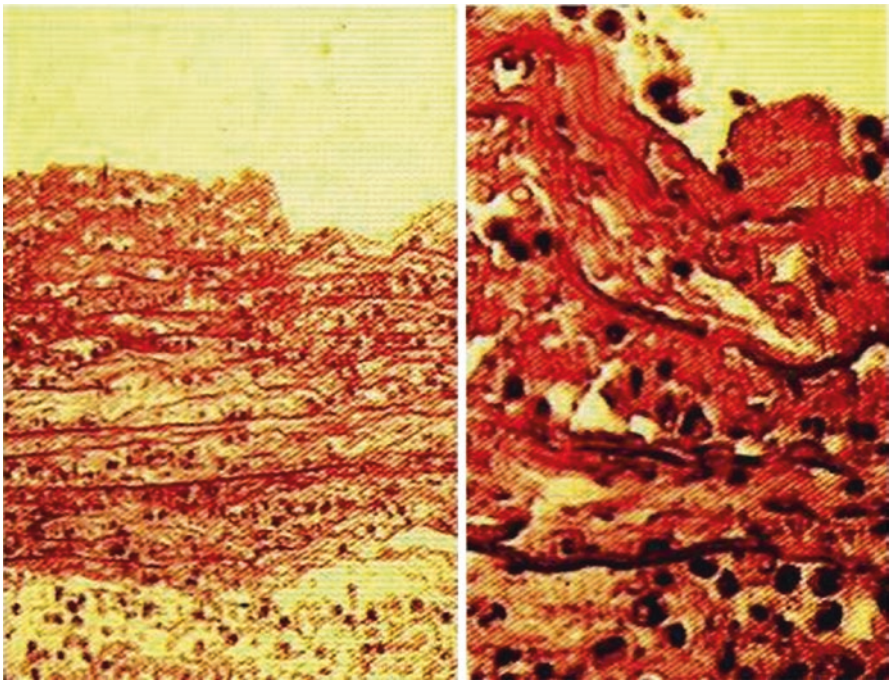

Fig. 3.7 Panarteritis—mixed inflammatory infiltrate. Stained with hematoxylin-eosin (*HE*)

fibroblasts causing hyperplasia, narrowing of vessel lumen, and intensive angiogenesis [33]. Unlike normal arteries, in which vasa vasorum are restricted to the adventitia, in case of GCA, capillaries emerge in the media and the intima [34].

Inflammatory damage in GCA is segmental. The intensity of inflammation varies in different parts of the same artery as well as between different blood vessels at different stages of the disease over time. Moreover, a classic picture of granulomatous inflammation can be seen only in about 50% of patients, whereas in other patients, panarteritis with mixed inflammatory infiltrate consisting of polymorphonuclear leukocytes with some neutrophils or eosinophils without giant cells can be found [35]. Panarteritis consists of leukocytes, lymphocytes, and plasma cells, as shown in Fig. 3.7 in case of our patient.

3.2.4 Clinical Picture of GCA

The onset and course of GCA are individual. Patients can suffer from headache or rheumatic joint and muscle difficulties similar to those of PMR (Table 3.1). Typical features of disease are headache as well as *painful swelling above the temporal artery* in elderly people (Fig. 3.8). As other medium or large arteries can be affected, clinical picture may vary accordingly. Other symptoms include nausea, lethargy, fever, claudication pain in jaws or tongue, chronic throat pain, and painful scalp induration. Headache is usually localized in the area of temporal artery, and it can

Table 3.1 Clinical picture of the giant cell "temporal" arteritis

1.	Headache
2.	Painful induration and flush above temporal artery
3.	Claudication pain in jaw muscles and/or tongue
4.	Chronic throat pain
5.	Visual symptoms with following blindness
6.	Polymyalgia rheumatica
7.	Raynaud's phenomenon, paresthesias, claudication in extremities
8.	Dissecting aneurysm of aorta, rupture of aorta
9.	Signs of myocardial ischemia
10.	Signs of cerebral ischemia

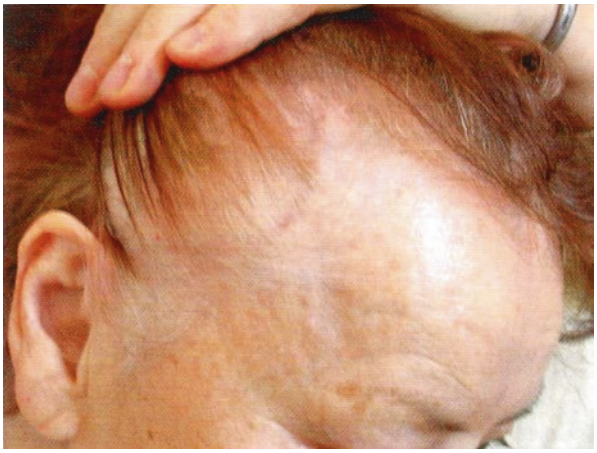

Fig. 3.8 Enlarged temporal artery in a female patient with GCA

radiate down into the neck, cheeks, jaw, or tongue. Pressure sensitivity, induration, flushing, and hair loss above temporal artery can develop later. Development of the first symptoms is usually acute, sometimes dramatic; however, some patients experience only general symptoms like weight loss, fever, weakness, and anorexia. In the latter patients, the diagnosis may be very difficult.

The most serious complication of GCA is *vision loss* occurring acutely, and both eyes can be affected consecutively in a short-term interval. Although visual symptoms can appear rapidly resulting in a dramatic vision loss, the most of patients suffer for a few months from the permanent ophthalmologic symptoms such as vision impairment or blurred vision. This fact only accentuates a need for symptom search and immediate therapy. Vision loss is a consequence of ischemic neuritis of the optic nerve or the central retinal artery occlusion.

Damage of aorta and its branches is observed in approximately 10–15% of patients with GCA, and the symptoms of damage of large arteries include Raynaud's phenomenon, paresthesias, and claudication in extremities. Life-threatening aorta damage can be a consequence of *dissecting aneurysm or rupture* of the aorta [36].

In patients with GCA, the occurrence probability of thoracic aorta aneurysm is 17.3-fold higher and abdominal aorta aneurysm is 2.4 times higher [37].

Lesions of coronary arteries are not often presented, but in the literature there are data about deaths in consequence of acute myocardial infarction [38–40]. Damage of carotid and vertebrobasilar arteries can be manifested by cerebral infarction [9] as well as by other neurological symptoms such as distraction, dementia, depression, tinnitus, hearing impairment, mononeuritis multiplex, peripheral neuropathy, and impairment of cranial nerves, e.g., paresis of the oculomotor nerve [41].

Impairment of upper and lower extremities is rarely found in GCA. Clinically, it is manifested by development of claudications or by sudden decrease in the claudication distance. Claudication is mostly bilateral. Critical limb ischemia is rarely found. In the literature only a small number of patients with *peripheral arterial diseases* (PAD) with limb ischemia together with histologically confirmed findings of GCA has been described so far [42–45]. But a recent meta-analysis demonstrated a statistically significant increased PAD risk among patients with GCA with 88% excess risk [46]. Although overt and clinically evident vasculitis of lower extremity in patients with GCA is uncommon, studies using ultrasonography and position emission tomography (PET) revealed that the prevalence of lower limbs involvement in GCA may be clinically underestimated [47].

3.2.5 Diagnosis

The principal clinical symptoms of GCA include a swollen and painful temporal artery, claudications in jaw muscles, diplopia, blindness, and PMR associated with high erythrocyte sedimentation rate. In laboratory testing, a higher erythrocyte sedimentation rate is observed in GCA (usually a value of more than 50 mm/h when using Westergren's method), as well as elevated C-reactive protein, normocytic normochromic anemia, elevated alkaline phosphatase, mildly elevated hepatic transaminases, elevated platelets, and lower serum albumin [48]. A few patients were described with low erythrocyte sedimentation rate [27]. This is important in cases when other symptoms indicate GCA diagnosis; hence a normal sedimentation rate does not delay the therapy.

In 1990 American College of Rheumatology developed classification criteria for GCA diagnosis (Table 3.2) based on a comparison of 214 GCA patients with a

Table 3.2 Classification criteria for GCA diagnosis (according to American College of Rheumatology, 1990)

1. Onset of disease in people older than 50 years
2. New onset or new type of localized headache
3. Pressure painfulness of temporal artery or lower pulsation of temporal artery
4. Higher erythrocyte sedimentation rate (over 50 mm/h)
5. Positive histological findings in biopsy

group of 593 patients with other forms of vasculitis [48]. At least three of five classification criteria must be met for diagnosis of GCA. The presence of three out of five criteria is associated with 93.5% sensitivity and 91.2% specificity for GCA diagnosis. Evaluation of the diagnostic criteria is simple, as, in addition to biopsy, it requires only clinical examination. Biopsy is the only invasive method, performed in local anesthesia, and it is associated with minimal complications. In one meta-analysis, jaw claudication and diplopia were the most predictive findings with biopsy-proven GCA [49]. There is no pathognomonic laboratory test or marker to identify GCA.

Temporal artery biopsy (TAB) is considered the gold standard for the diagnosis. But due to the segmental nature of the disease, inadequate sampling may yield false-negative results being as high as 40% [50]. *Duplex ultrasound* of the temporal artery has gained increasing attention. Based on the literature review, it has been concluded that ultrasonography should be the first choice test in GCA patients [51]. Proposed diagnostic algorithm based on clinical investigation (clinical criteria pointing: jaw claudication 2 points, diplopia 2 points, elevated ESR 1 point, localized headache 1 point, age over 50 years 1 point) and ultrasound investigation is seen in Fig. 3.9. Ultrasound was found to be 86% sensitive and 85% specific. Diagnosis of GCA in patients with a typical clinical

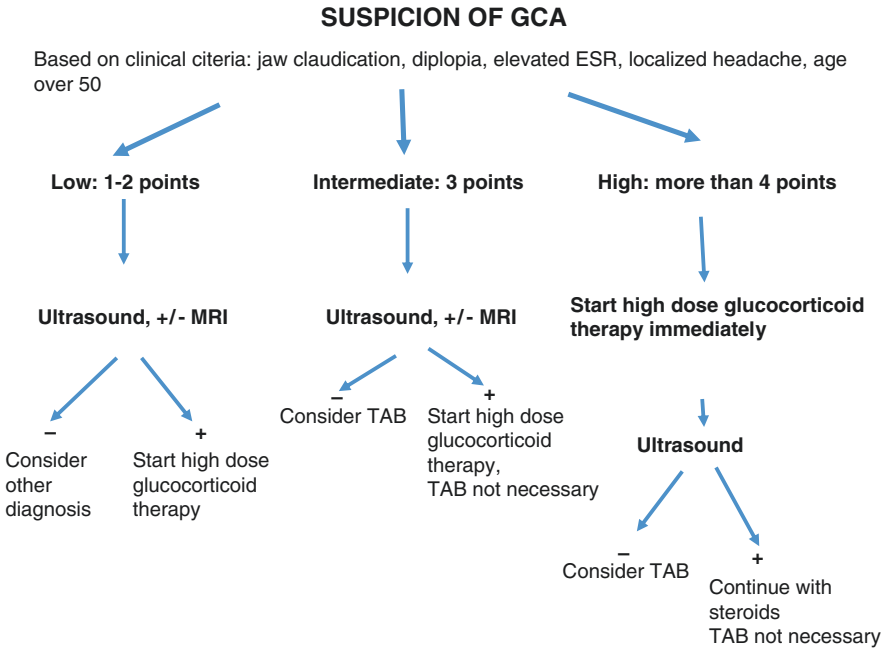

Fig. 3.9 Proposed diagnostic algorithm based on clinical investigation (*clinical criteria pointing*: jaw claudication 2 points, diplopia 2 points, elevated ESR 1 point, localized headache 1 point, age over 50 years 1 point) and ultrasound investigation (according to ref. [51])

constellation can be made solely on the basis of sonographic findings. Typical ultrasound sign of GCA is mainly hypoechogenic ringlet ("halo") shown around constricted lumen of the affected part of the artery, as well as typical stenosis and occlusions.

It is important to look for pathological changes also in other arteries, not only in the temporal artery, since the damage to large arteries can result in fatal consequences. It is also necessary to measure blood pressure on both upper extremities. Ultrasound and angiographic examination are the methods enabling quantification of the scope of damage to the artery system [52]. Angiography shows smoothly outlined stenosis and mildly dilated segments, sometimes occlusions. While angiography identifies mainly changes of the artery lumen, the changes of the wall of large arteries are very well demonstrated by CT [53], MRI, and PET [51].

MRI accurately demonstrates vascular lesions in temporal arteritis. It also has the added benefit of visualizing other arteries, like aorta and its branches. The pooled results from four studies show MRI in the evaluation of GCA to be sensitive in 79% and specific in 84% [51]. But MRI is not readily available in all hospitals; therefore, duplex ultrasound should be utilized first. *PET scan* has been demonstrated to be ineffective in measurement small in size (less than 5 mm in diameter), and for this reason it is not useful in evaluating the branches of the external carotid artery (e.g., temporal artery). Also, PET is not specific to vasculitis alone but to inflammatory processes including atherosclerosis.

Final diagnosis is determined by findings of typical panarteritis in biopsy of the temporal artery or an artery affected by another disease and by a negative muscle biopsy (differential diagnosis especially in PMR). Typical histopathological changes in GCA are a granulomatous inflammation, a presence of multinucleated giant cells mainly in the media, atrophy of smooth muscles and a destruction of elastic fibers, dissection and fragmentation of the internal elastic lamina, as well as calcium deposition in the internal elastic lamina and a new blood vessel growth (neovascularization). As artery damage is segmental and biopsy does not have to hit an affected area, it is recommended to investigate more sections from 5–8 cm long segment of temporal artery [54], at least 2–3 cm long segment. The biopsy should be performed before the corticosteroid treatment as it reduces the value of the examination. When the biopsy is done before the beginning of therapy, it can be useful in about 80% of cases; when the biopsy is performed in the first week of treatment, it is usually positive in about 60% of cases; however, when it is performed the week after the full glucocorticoid therapy, it is positive only in 20% of patients [6].

In differential diagnosis of patients without any histological confirmation of GCA diagnosis, it is essential to exclude malignant and infectious diseases, hypothyroidism, and rheumatoid arthritis, as those diseases may be manifested by similar clinical or laboratory symptoms such PMR or GCA. In case of damage of large and medium arteries, it is necessary to consider possible contribution of atherosclerosis. It is important to note that arteries can be affected at the same time by vasculitis, as well as by atherosclerotic process [55].

3.2.6 Therapy

PMR and GCA are very sensitive to glucocorticoid therapy. Withdrawal of muscle pain and rigidity in 24–48 h after corticoid administration is actually a diagnostic test [56]. Treatment should begin with the dose of 40–60 mg of prednisone with the following consistent dose reduction of the drug to daily maintenance dosage of 7.5–10 mg, while it is necessary to increase the dose, when the symptoms reappear. Reduction of glucocorticoid dose should not be faster than 5 mg per week, and at the end of the first month, it should not be lower than 20 mg per day. Sometimes, it is necessary to use a higher dose than 60 mg in the form of pulse therapy, mainly in the case of vision impairment and threatening amaurosis [57].

Administration of glucocorticoids at a sufficient dose leads to resolution of clinical symptoms and decrease in erythrocyte sedimentation rate as the drugs improve the function of endothelial cells and reduce inflammatory response [58]. GCA tends to have a fluctuating clinical course with alternating periods of exacerbation and remission of the disease. Glucocorticoids are effective in suppression of clinical symptoms of GCA and also in prevention of visual impairment.

As there is no laboratory test predicting therapy effectiveness, the recommended average therapy duration varies among studies. Although in some patients glucocorticoids during the first 6 months can be sufficient, the recommended period of therapy is at least 2 years in total. As 20–50% of patients treated by glucocorticoids suffer from side effects, e.g., compression vertebral fractures in 26% of patients, it is still necessary to find a drug dose sufficient enough but with minimal side effects. After the initial dose of 40 mg of prednisolone daily, Bengtsson [9] gradually reduced the dose to 2.5 mg daily, and this was followed by a withdrawal of prednisone treatment when after a month of such a minimal maintenance dosage clinical symptoms did not reappear. However, a relapse occurs in about 50% of patients on such a therapy regime, and it is necessary to restart prednisone therapy again at a dose of 10–15 mg daily with gradual reduction to 2.5–5 mg daily during one or two months.

A combined therapy of glucocorticoids with azathioprine is used rarely with possibility to lower glucocorticoids doses. According to some case reports of patients resistant to glucocorticoids, methotrexate was proved effective in GCA therapy as well. In some cases of extracranial GCA, it is possible to use also interventional radiological or surgery methods, e.g., angioplasty in the therapy [59].

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Coronary Artery Vasculitis and Atherosclerosis in Giant Cell Arteritis

4

Viera Štvrtinová, Jozef Rovenský, and Alena Tuchyňová

Increased incidence of coronary artery disease (CAD) has been observed in several chronic vasculitic and inflammatory syndromes, such as systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, or idiopathic inflammatory myopathy [1, 2]. EULAR guidelines for the management of chronic inflammatory diseases recommend that patients with these disorders should receive screening for cardiovascular diseases [3]. Giant cell arteritis (GCA) is a primary systemic vasculitis affecting especially older persons. GCA is closely related to polymyalgia rheumatica (PMR). One third or even one half of the patients diagnosed with GCA will also have PMR [4]. The inflammatory nature of both conditions (GCA and PMR) might lead to an increased risk of coronary artery vasculitis or enhance the risk of coronary atherosclerosis.

Myocardial ischemia and its extreme consequence, acute myocardial infarction, are generally accepted to be a result of transient or prolonged discrepancy between real myocardial needs for oxygen and the actual blood flow through the coronary arteries into the cardiac muscle. There may be a variety of reasons for insufficient blood supply into the coronary arteries. In industrialized countries, coronary heart disease (CHD) is caused by atherosclerosis in more than 90% of the cases: it should

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Table 4.1 Causes of myocardial ischemia (adjusted according to Cheitlin and Virmani [5])

1. Coronary atherosclerosis
2. Other diseases involving coronary arteries – arteritis (occurring in the course of primary and secondary vasculitis) – metabolic disease (mucopolysaccharidoses, homocysteinuria, Fabry's disease, amyloidosis, pseudoxanthoma elasticum, etc.) – compression of the coronary artery from the outside (e.g., by tumor)
3. Coronary artery aneurysms
4. Coronary artery thrombosis
5. Coronary artery spasms
6. Coronary artery embolism
7. Congenital abnormalities of coronary arteries
8. Injuries and dissections
9. Disproportion between oxygen needs and supply (aortic stenosis, aortic insufficiency, thyrotoxicosis, pheochromocytoma, etc.)
10. Syndrome X (small vessel disease)

be borne in mind however that there is a wide range of other pathological processes that eventually may result in myocardial infarction [5] (Table 4.1).

Inflammatory affection of the coronary arteries may present a life-threatening condition and the underlying reason for CHD in all age groups. Since the epicardial coronary arteries are not easily accessible to biopsy, as well as the pathogenesis and classification of various forms of vasculitis are rather confusing, diseases involving the coronary arteries are rarely diagnosed correctly during the lifetime of the patients. However, a correct and timely diagnosis has become vitally important not only for the necessity to aggressively manage some "malignant" forms of vasculitis by immunosuppressive therapy but also because a needless administration of such therapy may lead to serious complications and adverse effects. It is therefore rather crucial to make an early distinction between vasculitis, i.e., inflammatory condition of the coronary artery, and atherosclerotic alterations since the management of the two conditions would be approached differently [6].

On the other hand, underlying vasculitis may enhance atherogenesis and the development of atherothrombosis. Smoking, hyperlipidemia, hypertension, and diabetes mellitus as the major risk factors for the development and progression of atherosclerosis cannot explain atherosclerosis in many patients. A number of additional risk factors, which might be affected by systemic or local inflammation, have been identified during recent years-including elevated levels of homocysteine, lipoprotein (a), oxidative or enzymatic modifications of lipoproteins, estrogen deficiency, hypercoagulability, and last but not least infection [7, 8]. Increasing evidence suggests that atherosclerosis is a chronic inflammatory disease developing in response to certain specific injury of vascular wall. Vascular wall inflammation plays a significant role in both the development of atherosclerosis and during the later stages when inflammation is considered to be the reason for the instability of the atherosclerotic plaque. Macrophages, endothelial cells, smooth muscle cells, and activated

lymphocytes are the principal constituents of the atherosclerotic plaque. Similar to an inflammatory process, there is an interaction between effector cells of the immune response and the production of soluble mediators (cytokines, chemokines, and soluble adhesion molecules). Markers of systemic inflammation such as C-reactive protein or serum amyloid A appear to predict cardiovascular events in healthy men, and aspirin seems to significantly reduce the risk of myocardial infarction in individuals with high CRP levels only. Statins in addition to reduction of blood lipid levels modify endothelial function, inflammatory responses, plaque stability, and thrombus formation and thus reduce the risk of cardiovascular complications.

For the human vasculitides as well as atherosclerosis, both autoimmune and infectious causes have been proposed [9]. The primary symptoms of many vasculitides resemble those of infectious diseases, and moreover, vasculitis is a well-documented manifestation of infection by some known microbial agent. In addition, in chronic or "extinguished" syphilitic arteritis, alterations of the intima resemble atherosclerotic changes, and atherosclerotic lesions may frequently be layered onto old syphilitic lesions. The organisms implicated (*Chlamydia pneumoniae*, *Helicobacter pylori*) as well as herpes viruses (mainly cytomegalovirus) are ubiquitous, and this has raised question whether they may in some patients enhance inflammation in atherosclerosis or in others, e.g., in patients with altered immune function, lead to systemic vasculitis. It however remains unclear whether infectious agents act in the development of atherosclerotic lesions as a cause or as a cofactor or whether they are present just as an innocent commensal.

In our group of 23 patients (15 females and 8 males) with the diagnosis of GCA (Table 4.2), 4 patients developed myocardial infarction, 2 patients suffered stroke, and 1 patient had both myocardial infarction and stroke. One female patient developed peripheral arterial obliterative disease of the lower extremities. Of 23 patients with the diagnosis of GCA, 9 patients had polymyalgia rheumatica [10]. The GCA diagnosis was established according to the American College of Rheumatology classification criteria, and in 21 patients (of 23) the diagnosis was confirmed by histology.

The involvement of the coronary arteries in GCA patients is rarely recognized, though deaths have been reported due to acute myocardial infarction [11]. Freddo et al. [12] suggest that myocardial infarction may be a more common early complication of giant cell arteritis than appreciated and can occur despite administration of high-dose corticosteroid therapy.

In England a large analysis of an association between PMR and GCA and risk for cardiovascular diseases, based on Cardiovascular disease research using Linked Bespoke studies and Electronic health Record (CALIBER) data, was done. This analysis included 9776 patients with the diagnosis of PMR, 1164 patients with the diagnosis of GCA, and 627 patients with both diagnosis of PMR+GCA. Data from primary care as well as hospital and mortality data, from 1997 till 2010, were included in the analysis. In this large population-based cohort, the presence of PMR and/or GCA was not associated with an increased risk of cardiovascular events [13]. But incidence of cardiovascular events was higher in the GCA than in the pure PMR

Table 4.2 The group of our patients with giant cell arteritis

Patient	Gender	Year of birth	Age at the onset	Histology	Stroke	IM	PMR
1	Male	1926	74	+	0	0	0
2	Female	1919	76	+	0	0	0
3	Female	1931	66	+	0	+	0
4	Female	1925	73	+	0	0	0
5	Male	1941	51	+	0	0	0
6	Female	1921	75	+	0	0	0
7	Female	1924	72	+	0	0	0
8	Female	1939	54	+	0	0	0
9	Male	1926	70	+	0	0	0
10	Female	1917	81	+	0	0	0
11	Female	1919	55	+	0	0	0 PAOD
12	Female	1924	73	+	0	+	0
13	Female	1914	84	+	0	0	0
14	Male	1926	64	Not done	+	0	1
15	Male	1923	77	+	+	+	0
16	Female	1936	56	Not done	0	0	1
17	Female	1912	61	+	0	++	1
18	Female	1926	58	+	0	0	1
19	Female	1920	55	+	0	0	1
20	Female	1912	64	+	0	0	1
21	Male	1919	67	+	0	0	1
22	Male	1903	72	+	0	0	1
23	Male	1903	75	+	0	0	1

IM myocardial infarction, *PMR* polymyalgia rheumatica, *PAOD* peripheral arterial obliterative disease of the lower extremities

group (71 vs. 55/1000 person-years). Also coronary death was higher in the GCA group (30/1000 person-years) comparing to pure PMR group (24/1000 person-years) or control group free of PMR and GCA (26/1000 person-years). Study limitations include the possibility of PMR/GCA misclassification, due to the fact that in this study PMR/GCA diagnosis was based on recorded physician diagnosis in primary care and hospitals. Information on American College of Rheumatology classification criteria or histology was not available in this study.

Several studies have found a lower cholesterol level and lower occurrence of diabetes mellitus (DM) in GCA patients [14, 15]. The reason of lower prevalence of diabetes in GCA patients is not clear. One hypothesis is that patients with DM may have a decreased responsiveness of T cells to the inciting antigens being presented by the dendritic cells of the arterial adventitia [16].

Just recently (in 2015) a meta-analysis of coronary artery disease in GCA was published [17]. Six studies with 10,868 patients with GCA and 245,323 controls were included into this meta-analysis. The pooled risk ratio of CAD in patients with GCA was 1.51 and did not achieve statistical significance (95% CI, 0.88–2.61), but

the statistical heterogeneity was high. The main source of this heterogeneity was difference in CAD definition. Thus in contrast to other chronic systemic inflammatory diseases [1, 2, 18], in this study an increased CAD risk among patients with GCA was not observed. The main difference between GCA and other inflammatory chronic vasculitic syndromes (e.g., systemic lupus erythematosus, rheumatoid arthritis) is the age of disease onset. This difference is what we should take into account.

GCA is the only systemic vasculitis which starts in the elderly. Thus the pathophysiological mechanism of vessel wall damage in GCA could differ from those seen in SLE or RA. In view of the high age of patients with GCA, their coronary artery disease may be attributed to atherosclerotic alterations of the coronary arteries. However, vasculitis can set in the vascular wall already damaged by the atherosclerotic process, and the inflammatory response can be triggered by a so far unknown mechanism. Moreover, when healed up, giant cell arteritis may only hardly be distinguished from atherosclerosis, and some pathologists claim that atherosclerosis and giant cell arteritis may be based on a common pathological process. On the other hand, patients with GCA might not live long enough after disease diagnosis to observe the detrimental effect of chronic inflammation on their coronary arteries [17].

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Immunocompetent Cells and Their Role in Polymyalgia Rheumatica and Giant Cell Arteritis

5

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Giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) are two closely related syndromes affecting elderly people. Dramatic changes with age are characteristic for immune system. Immunosenescence has been recognised as component autoimmunity. General experience says that with age the capacity to generate protective immune response declines, whereas reactivity to autoantigens increases.

GCA and PMR are an inflammatory vasculopathy mediated by pathogenic condition of unknown aetiology. Recent studies have shown that participating in the pathological process are innate and adaptive immune cells, as well as vascular cells. The pathological finding in GCA is granulomatous infiltrates in the wall and medium-sized arteries [1]. Immunohistochemical studies have shown that $CD4^+$ T lymphocytes and monocytes/macrophages are the dominant cell populations in the infiltrates. Weyand et al. [2] provided evidence recently for clonal expansion of $CD4^+$ T cells in vascular lesions. A minority of tissue-infiltrating T cells was present in multiple copies, and $CD4^+$ T cells with identical T cell receptor β chains were isolated from distinct vasculitic foci. Clonal expansion of $CD4^+$ T cells and restriction in the polymorphism of antigen-driven HLA-DR molecules support the model that GCA is an antigen-driven disease in the wall of medium-sized arteries. Carmona

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et al. confirm the association between HLA-DRB1*04 alela and GCA. In addition to genetic predisposition, GCA similarly as other autoimmune diseases may be influenced also by environmental factors, including viral agents. The presence of VZV antigens in TAs and subsequent histopathological changes in the patient samples were documented in two studies [3, 4]. Interaction of genetic and environmental factors leads to dysregulation of autoimmune response.

Cytokines play an important role in the regulation of immune responses. Markedly elevated interleukin-6 (IL-6) and IL-1 receptor antagonist concentrations were found at the time of PMR diagnosis, thus prior to start of glucocorticoid therapy. On the other hand, systemic concentrations of other anti-inflammatory cytokines, such as tumour necrosis factor (TNF) and IL-1 beta, were comparable with those measured in healthy controls [5].

Systemic concentrations of IL-6 are elevated in GCA and PMR. After initiating corticosteroid therapy, IL-6 concentration abruptly returns to normal and remains suppressed as long steroid therapy is continued. IL-6 in the media of vessels is mainly produced by macrophages, whereas it is also produced by fibroblasts in the intima. Expression of the gene for IL-6 was not observed in endothelial cells or giant cells. As a result of glucocorticoid therapy, systemic concentrations of IL-6 decrease. IL-6 production in the involved arteries may thus contribute to general symptoms of GCA [6]. In GCA and PMR patients, expression of IL-6 and IL-1 beta was observed in about 60–80% circulating monocytes. It has been suggested that GCA possibly consists of two components, inflammatory reaction of the vascular wall and systemic monocyte activation, while in the case of PMR, there probably is systemic monocyte activation without vasculitis [7]. IL-6 together with BAFF (B cell activation factor) modulates closely with disease activity in GCA and PMR. Van der Geest et al. [8] compared 26 serum markers and found out that BAFF, IL-6 and CXCL9 levels were elevated in newly diagnosed GCA and PMR patients. Serum BAFF and IL-6, but not CXCL9, were attenuated upon glucocorticosteroid-induced remission and showed the strongest association with disease activity in both GCA and PMR patients. IL-6 has been linked to the enhanced Th17 response in GCA and PMR. Finally, clinical studies demonstrated high circulating levels of Th17 cells and related cytokine IL-17 in patients with different forms of vasculitis [9–12]. Frequencies of Th17 cells, as assessed by flow cytometry, are increased up to tenfold in the blood of patients with GCA [9, 12, 13]. Th17 cells are part of the cellular infiltrates in the arteries. Prior to therapy, IL-17-producing T cells were mixed with IFN-γ-producing TH1 cells to create the granulomas. Arteries from treated patients contained few TH17 cells, but were populated by TH1 cells [9].

Th2-derived cytokines have been previously demonstrated to be consistently absent in GCA [14, 15]. Ciccia et al. [16] showed, however, that IL-33 (a cytokine involved in promoting the Th2 response) is overexpressed in the inflamed arteries of GCA patients and is accompanied by strong M2 polarisation [17]. Furthermore, IL-33 has recently also been associated with the secretion of IL-9 by human $CD4^+$ T cells isolated from peripheral blood [18]. Although the functions of Th9 cells have not been completely clarified, they seem to be involved in several types of inflammatory disease in both mice and humans [19]. Whether IL-9 and Th9 cells are

involved in the pathogenesis of GCA is not known. IL-9 and Th9, but not Th17, polarisation predominates in inflamed arteries of GCA patients with inflammation restricted to the periadventitial small vessels. Conversely, a more intense Th17 polarisation with weak IL-9 expression predominates in GCA arteries with inflammation restricted to the vasa vasorum. Finally, a concomitant strong Th9 and Th17 response was observed in the more inflamed arteries displaying transmural inflammation and especially in those arteries with a granulomatous reaction. Ciccia et al. [16] for the first time demonstrated a putative pro-inflammatory role for IL-9 and Th9 cells in the pathogenesis of GCA. They have also provided the first evidence that distinct populations of potentially autoreactive T cells expressing particular cytokines (Th17 vs. Th9) characterise patients with particular histological subsets of GCA and may thus contribute to the heterogeneity of tissue lesions observed in these patients. The concomitant presence of a Th9 response may be responsible for the chronicity of tissue damage with the emergence of more severe tissue inflammation.

Inflammation in the portal and lobular region of the liver with focal liver cell necrosis can be observed, sometimes accompanied with the formation of small epithelioid cell granulomas. Subtle inflammatory changes may be visible in the synovial tissue: the synovial fluid shows a slight inflammatory activity.

Besides T lymphocytes, macrophages are the second components of the vascular lesions. Their role in the inflammatory events in the arterial wall is unclear, although during the recent 10 years also, involvement of vascular dendritic cells in the inflammatory process has been documented. In vasculitic lesions, these vascular dendritic cells get activated, increase in number and are distributed throughout the wall and are an absolute requirement to sustain the disease process [20]. Subsequently, $CD4^+$ lymphocytes and macrophages get involved in the process. Several functions of macrophages could be of significance in initiating and maintaining the tissue infiltrate in GCA. Data of Wagner et al. [21] support the view that an additional component of systemic monocyte activation exists. It is possible that the activation of circulating monocytes results from an immune response to the same antigen in other tissues than the temporal artery, e.g. lymph nodes and bone marrow. Functional activities of T cells and macrophages that accumulate in the arterial wall have been determined by analysing the transcription of cytokines and monokines in extract from temporal artery biopsies. Compared with noninflamed temporal arteries, inflamed specimens contain the T cell products IFN-γ and interleukin-2 and the $CD68^+$ macrophage products IL-1 beta, IL-6 and transforming growth factor-β (TGF-β). TGF-β was most abundantly found and was produced in conjunction with, but also in the absence of, IL-1 β and IL-6. Comparison of circulating and tissue-infiltrating $CD68^+$ cells in GCA patients revealed two interesting findings. Circulating $CD68^+$ cells were activated in high frequency, and the composition of the peripheral and tissue compartments was clearly distinct, raising the possibility of selective recruitment into the vascular lesions. The presence of similar frequencies of $CD68^+$ $IL\text{-}6^+$ cells in PMR and GCA patients demonstrates that the activation of peripheral monocytes does not require the vasculitic component of the disease. Whether the availability of IL-6- and IL-1 β-producing monocytes in blood is

prerequisite, preceding the formation of the vasculitic lesions is possible but unanswered [21]. In patients with PMR, cytokine mRNA can be detected in temporal artery tissue specimens despite the lack of microscopic evidence of tissue-infiltrating cells [2]. The low number of tissue-infiltrating macrophage and sensitivity of the polymerase chain reaction may explain the finding of the low frequency of IL-6 in tissue of PMR patients. In contrast to macrophage activation, the T cell response appears to be quantitatively, but also qualitatively, different on the two diseases. Although patients with GCA and those PMR did not differ in their in situ production of IL-2, the presence of INF-γ sequences was significantly different. IFN-γ mRNA is more easily detected in active T cells than in IL-2 mRNA, indicating that the also absence of INF-γ in the tissue of PMR patients is of biological significance and is not a result of insufficient sensitivity. IFN-γ is crucial for macrophage activation and for granuloma formation. Thus the production of IFN-γ may be essential for the development of vasculitis. Patients with PMR may lack an important amplification mechanism in their local immune response in the vasculitic lesion [2]. Tissue synthesis of tumour necrosis α and granulocyte-macrophage colony-stimulating factor has not been informative in distinguishing normal and inflamed temporal arteries. Clinical experience has shown that it is often difficult to document the presence or absence of vasculitis in patients with PMR. Weyand et al. [2] had shown that PMR and GCA share multiple pathogenic features in addition to similarities in the clinical presentation. Both diseases have in common an association with selected HLA-DRB1 alleles in particular the HLA-DRB1*04 alleles [22, 23].

Wagner et al. [21] have searched for $CD4^+$ interferon-γ T cells in temporal artery specimens. Interestingly, only 2–4% of all T cells in the arterial wall have the capability of releasing IFN-γ. Although this observation raises the point that only small subsets of T cells may be disease relevant, these frequencies are compatible with the local activation of antigen-specific T cells. Indeed, $CD4^+$ IFN-y^+ T cells in GCA lesions display several features that identify them as the T cells recently stimulated by specific antigen. Clonal expansion T cells were not detected in peripheral blood, indicating that there is accumulation of such T cells in tissue. Biopsy samples of temporal arteries showed mononuclear cell, T cell and macrophage infiltration in the vascular wall and disturbed lamina elastica of the temporal artery. IgG, IgM and IgA and complement and fibrinogen deposits were identified in the lesions. Moreover, enhanced IL-1 beta and interferon gamma production and slightly reduced production of TNF were identified [24]. IFN-gamma seems to be an important factor, which modulates hyperplasia of the intima in the inflammation-affected vessels [25].

Evidence for a pathogenic role of antibodies and immune complexes is missing. B cells are extremely rare in the vascular lesions, which is consistent with the lack of antibody production and of immune complex deposition or hypergammaglobulinemia in GCA. Even in patients with GCA and concomitant chronic lymphatic leukaemia, in which B cells are typically found to infiltrate diffusely into tissue, the temporal arterial lesions contain very few B cells, raising the possibility that vasculitic infiltrates are a disfavoured environment for B cells [26]. B cells are a minor cell population in granulomatous infiltrates, and in immunohistochemical studies,

B cells are scarcely detected in temporal artery biopsy specimens [26]. The presence of high levels of autoantibodies in the serum of patients with GCA and PMR suggested the idea that there could be a B cell activation in these patients. The number of B cells is decreased during active disease, and in particular it seems that effector B cells are redistributed in a still unidentified site during active disease and return to normal during steroid-induced remission [27]. Early studies have indicated that deposits of immunoglobulins are present in the inflamed temporal arteries of GCA patients [28, 29]. Emerging data indicate that B cells not only produce antibodies but also modulate T cell responses by secreting pro-inflammatory and anti-inflammatory cytokines such as tumour necrosis factor-α and interleukin-10, respectively [30–32]. Furthermore, effector B (Beff) cells can potentiate T cell-mediated autoimmunity via secretion of IL-6. B cells from GCA patients with active disease had an enhanced capacity for IL-6 production, and B cell-activating factor was strongly associated with disease activity [8, 33]. Van der Geest et al. [33] first investigated whether the circulating B cell pool was perhaps replenished by immature, transitional B cells from the bone marrow. Since the numbers of transitional B cells were even further decreased in the peripheral blood of treated patients with GCA or PMR in remission, it seemed highly unlikely that the circulating B cell pool was repopulated by newly produced B cells from the bone marrow. Next, they assessed whether B cell numbers were replenished through compensatory hyperproliferation of circulating B cells in patients with GCA or PMR in remission. Their data indicated that B cells were redistributed during active GCA and PMR and returned during remission. Modulated serum levels of BAFF suggested that B cells were redistributed rather than marginalised in patients with newly diagnosed GCA or PMR [33].

Accumulating evidence indicates that GCA represents the consequences of a local immune to a disease-inducing antigen, and it is considered the best example of T cell-mediated vasculitis [15]. In the vasculitic lesions, which also express activation surface markers, undergo clonal proliferation in the inflammatory lesions of temporal artery.

TCR repertoire has been examined in patients with PMR and GCA in a number of recent studies [14, 34, 35]. In both of them, patients with PMR and GCA carried multiple expanded T cell populations, especially within the $CD8^+$ T cell subset. Although a significant number of these selected clonotypes decreased in size with high-dose steroid treatment, all of them persisted despite successful control of the disease with treatment [36]. Because GCA and PMR display strict age dependence, it can be hypothesised that age-related changes in the TCR repertoire render individuals susceptible to the disease. To address this hypothesis, Martinez-Taboada et al. [14] have compared a cohort of 18 patients with GCA or PMR with 9 age-matched controls. The frequency of clonal expansion was not different in two cohorts. Sequence analysis of the CD8 clonotypes indicated a distinct 1β gene segment usage in the patients compared with normal control. In individual patients, preferential rearrangement of selected 1β gene elements was found, raising the possibility that a jp-specific mechanism was involved in driving the clonal proliferation of $CD8^+$ T cells in GCA and PMR. Because oligoclonality in the CD8 subset

persisted despite successful treatment of the disease, Weyand and Goronzy [37] have proposed that such clonotypes are not directly involved in the disease process. However, the preexisting T cell repertoire might modulate an individual's risk of generating a pathologic T cells.

A recent study reported on the involvement of $CD8^+$ T cells in GCA pathogenesis through the implication of NKG2D, the ligand of MICA (major histocompatibility class I chain-related A), whose expression is increased in the arteries of GCA patients [38]. The expression of CCR7, CD62L, CCR5, CCR6 did not change, but the percentage of $CXCR3^+$ cells among total. $CD8^+$ T lymphocytes were significantly higher in untreated GCA patients than in control. Serum concentration of CXCR3 ligands (CXCL9, CXCL10 and CXCL11) was subsequently measured, and their levels were higher in untreated patients than in control, and the levels of these three chemokines significantly decreased after 3 months of glucocorticoid therapy. Furthermore, authors of the study observed $CXCR3^+CD8^+$ T cell infiltration and production of CXCL9 and CXCL10 in TABs. Altogether, these results suggest the recruitment of $CD8^+$ T cells in the arterial wall through an interaction between CXCR3 and its ligands. In a recent study, it was demonstrated that IFN-g, which is produced by Th1 cells, triggers the production of CXCL9, CXCL10, CXCL11 and CCL2 by vascular smooth muscle cells in temporal arteries from GCA patients [39]. CCL2 induces the recruitment of macrophages [38], whereas CXCL9, CXCL10 and CXCL11 induce the recruitment of any cells expressing $CXCR3^+$ such as $CD8^+$ T cells, as were demonstrated in the study of Samson et al. [40].

In contrast with studies [14, 41, 42], Lopez-Hoyos et al. [35] did not find a clear correlation between T cell expansions and disease activity. The analysed TCR repertoire of circulating T lymphocytes with nine BV-specific monoclonal antibodies accounts for about 40–50% of the total cell repertoire. Patients with active disease had higher percentage of CD47BV3"^{l}" T cells than healthy control. However, there were no differences between patients and controls in any of the TCR BV families of the $CD8^+$ subsets. A new analysis carried out in patients with PMR and GCA 6 months after steroid therapy, when they were asymptomatic, showed no significant changes in the distribution of the TCR BV expansions, suggesting that these expanded populations probably are not directly involved in the disease process [35]. However, much less is known about the role of circulating T cells in patients with GCA and PMR. The open question is about the number of circulating T cells and other subtypes in patients with PMR and GCA. When PMR/GCA patients' non-treatment was compared with controls, Macchioni et al. [43] observed a significant reduction in the absolute number and relative percentage of $CD4^+$ $CD8^+$, CD3 $HLA\text{-}DR^+$ and $CD3^+$ $CD16^+$ and/or $CD56^+$ cells. CD4/CD8 cell ratio was significantly higher in PMR/GCA patients compared to controls. No significant differences in the relative percentage and absolute number of the other lymphocyte subsets ($CD5^+CD20$~, $CD5^+CD20^+$, $CD3^+HLA\text{-}DR^+$, $CD4^+CD8^-$, $CD8CD57^+$, $CD8^+CD57^+$, $CD3CD56^+$) considered were observed when compared to controls. Some reports have described a decreased percentage of circulating $CD8^+$ cells before treatment and persisting for some months during corticosteroid therapy. $CD8^+$ T lymphocytes are involved in the pathogenesis of multiple autoimmune

diseases, including vasculitis [44, 45]. By production of IFN-gamma, $CD8^+$ expressing CD11b molecule may activate neutrophils and cause vascular inflammation [46] in primary active ANCA-associated vasculitis. The $CD8^+$ lymphocytes are heterogeneous in subphenotypes and functions. $CD8^+$ cells include T cells, which express high-density $CD8^+$ ($CD8^{bright+}$), and not T cells with natural killer (NK) activity, which express low-density $CD8^+$ ($CD8^{dim+}$). Boiardi et al. [47] reported the phenotypic characterisation of $CD8^+$ subsets of patients with active PMR. They found that the percentage $CD8^{bnght+}$ was significantly lower in patients with active PMR (44%) compared to controls matched for age and sex; both subsets of $CD8^{bright+}CD57^+$ and $CD8^+$ CD57 were significantly reduced. The absolute of $CD8^{bnght+}$ cells returned to the normal range after 3 months of steroid therapy. However, the absolute numbers of these subsets at the end follow-up (2 years) were lower to those of normal control. The changes in the absolute number of $CD8^{bnght+}CD57^+$ and $CD8^{bright+}CD57^-$ cells during the follow-up paralleled the variations of $CD8^{brigth+}$ cells. The percentage of $CD8^{bnght+}$ increased significantly after 1 year of steroid therapy compared to baseline values, but they remained significantly lower compared to controls for the entire 2-year follow-up period. The percentage of $CD8^{bnght+}CD57\sim$ cells increased significantly after 6 months of therapy, even if the first and second year values were significantly lower compared to the control. Andersson et al. [48] found normal numbers of $CD8^+$ and $CD4^+$ cells in patients with GCA before treatment, and Banks et al. [49] documented normal ratios of helper to suppressor cell. Other studies in patients with PMR and GCA have found a decreased percentage of $CD8^+$ cells [50–53], although Dasgupta et al. [50] and Elling et al. [52] also reported reduced absolute number of $CD8^+$ cells. Significantly reduced percentages and number of $CD8^+$ cells have been found in 40–80% of patients with PMR and GCA [52, 54–56]. All of the studies apart from the negative study by Andersson et al. [48] used mononuclear cells separated on Ficoll-Paque density gradient. This method selectively decreases the $CD8^+$ subsets than the whole blood analysis. This artefact would not necessarily affect samples form controls and patients to the same extent, so could distort the results. Patient $CD8^+$ cells might have intrinsic differences from control cells affecting their migration on a density gradient and might well also have differences due to a delay in processing compared with control cells. A marked decrease in the percentage of $CD8^+$ and $CD4^+$ cells has been shown in blood stored for 24 h when the Ficoll-Paque method was used, but not with whole blood lysis method [57]. Furthermore, a delay of more than 6 h before processing blood samples results in a considerable decrease in the absolute number of lymphocytes counted by automated haematology counters [58]. Such a delay might occur more often with patient sample than control samples, particularly in multicentre studies where patient blood samples may be transported from other hospitals for analysis. In their study in 1996, Elling et al. [59] documented that reduction of $CD8^+$ T lymphocytes correlated with carotid artery stenosis. In addition it was found out that their reduction after glucocorticoid therapy was associated with a risk of relapse and these patients needed a long-term corticosteroid therapy [59]. The role and significance of $CD8^+$ in GCA have not been fully clarified, yet. In their latest study, Samson et al. [12] have focused on $CD8^+$ T lymphocytes as a GCA prognostic factor. In addition to the

number of peripheral blood mononuclear cells (PBMC) and their cytokine production, they have examined also infiltration in temporal artery biopsy (TAB). They have detected no difference in CD3, $CD4^+$ and $CD8^+$ T lymphocyte percentage in untreated GCA patients as compared to control subjects. Analysis of subtypes has revealed a significantly higher level of cytotoxic CD 8^+ T lymphocytes (CTL), defined as $CD3^+CD8^+$ granzyme B^+perforin$^+$ in untreated patients as compared to control subjects. Together with correlation with CRP, fibrinogen level and higher CD63 expression on $CD8^+$ T lymphocyte membrane, this points to a marked activation of $CD8^+$ T lymphocytes. Immunochemical analyses of positive TAB in GCA patients have demonstrated transmural infiltration by CD4 cells as well as infiltration by $CD8^+$ T lymphocytes, again with cytotoxic signs—positive granzyme B and expression of TiA1 (T cell intracytoplasmic antigen), partially in the intima [27]. Strong $CD8^+$ T cell infiltrations in temporal artery biopsies are by Samson et al. [12] associated with a more severe disease. $CD8^+$ T cells that had exerted their cytotoxicity in the arterial wall re-enter the circulation [29]. The outcomes of recent studies published by Samson et al. [12] and Regent et al. [60] have shown that $CD8^+$ T cells have a limited TCR repertoire, which suggests that they were stimulated by one or more specific antigens that may originate from vascular smooth muscle cells or endothelial cells.

Although in fact other biological variables may be of major importance, it has been suggested that two populations of patients with PMR/GCA are present. A persistently reduced percentage of $CD8^+$ after 6 months of treatment has been correlated to more severe disease [56]. Reduced levels of $CD8^+$ cells and concomitantly reduced concentrations of $CD8^+$ cells have also been found in first-degree relatives of patients with GCA, indicating it to be a hereditary characteristic [61].

Corrigall et al. [62] on the basis of their results showed that patients presenting with a clinical picture of PMR can be divided into two groups on the basis of their pretreatment % $CD8^+$ T cells: one group with low $CD8^+$ cells have true PMR on follow-up, while the second, with normal % $CD8^+$, go to develop other diseases on follow-up, the commonest one being seronegative rheumatoid arthritis. A further group of patients identified as having normal values for % $CD8^+$ were later diagnostic as having various malignancies.

There is an evidence for associated changes in the distribution of T cell subsets in the circulating T cell compartment [63]. The significant findings as well as an inverse relation of naive and memory $CD4^+$ cells, normal expression of surface marker indicating activation of T cells and the severe depletion of $CD8^+CD28^+$ circulating T cells may contribute to the development of disease in two different ways. Firstly, it may reflect a possible infectious agent, especially a viral infection, as responsible for these syndromes. An increasing amount of epidemiological, clinical and laboratory evidence support this hypothesis [64]. Secondly, and not mutually exclusive from the first hypothesis, the loss expression of CD28 with ageing may contribute to state of immunodeficiency that may make a susceptible person prone to develop a disease [50].

The cellular players in GCA are known, but further studies are needed to deepen the information on them, and it gives new hopes to treatment. Several clinical trials

are currently exploring the use of cytokine blockers and of costimulatory inhibitors. Some currently available T cell immunosuppressants are used empirically in patients requiring long-term therapy, but their use has not been investigated in appropriately designed clinical trials.

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Genetic Factors in Giant Cell Arteritis and Polymyalgia Rheumatica

6

Vladimír Bošák

The etiopathogenesis of giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) remains unknown, although genetic, autoimmune and environmental factors have been implicated. Evidence points to a genetic predisposition in these syndromes. GCA and PMR are more frequent in Caucasians, especially in the countries of northern Europe and in some regions of the United States, in those with Scandinavian ancestry [1, 2]. Several cases of familial aggregation of GCA and PMR have been also reported [3, 4], and HLA typing studies have shown a consistent association of both syndromes with certain alleles of the HLA system [5].

Attention to HLA antigens in GCA and PMR has been paid since 1975, when the first study was published [6]. More than 50 various papers can be found in the literature focusing on this problem [5]. HLA-A, HLA-B, and HLA-C antigens have shown variable results, which suggest that a significant relationship is unlikely [5, 7, 8]. Negative results were obtained also with respect to HLA-DQ (genes DQB1*, DQA1*) and HLA-DP antigens [5, 9]. Positive findings were reported concerning HLA-DR antigens. GCA is the best example of an association between vasculitis and gene HLA-DRB1. Most studies have shown an association with alleles HLA-DRB1*04. PMR is associated with HLA class II genes, but this varies from one population to another. Relapses of PMR, however, have been found to be significantly more common in patients who have the HLA-DRB1*04 alleles [5, 7, 8, 10, 11]. The association between PMR/GCA and HLA-DR4 is typical predominantly for white Caucasian populations of Europe and North America, while such association could not be confirmed for Mediterranean populations-Italy, France [12, 13]. Both PMR and antigen HLA-DR4 are rare in black populations. For Caucasians, frequencies of HLA-DR4 (HLA-DRB1*04) in the patients range between 36% and 71%, depending on the studied population. Most studies have described an

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association of PMR/GCA with alleles DRB1*0404/04 and DRB1*0401 [10, 14]. The literature data also indicate an interaction between HLA-DRB1 and IL-4 that contributes to pronounced diseases' susceptibility [15].

Attention was also paid to the relationships with clinical symptoms and laboratory findings in GCA and PMR. A majority of the studies brought negative results, but some authors observed an association between HLA-DR4 antigen and visual symptoms in GCA and GCA resistance to corticosteroid therapy. Thus, it cannot be ruled out that HLA-DR4 may be a marker of the severity of the disease [16].

It should be mentioned in connection with HLA-DR4 that this antigen is also associated with rheumatoid arthritis (RA), in particular with the prognostically more severe forms of the disease. RA setting on at older age (≥60 years) on the other hand is clinically related to PMR, and it even seems to also have a similar immunogenetic characteristic—association with antigens HLA-DR1 and HLA-DR13/14 [9]. Literary data suggest that PMR, GCA and RA may differ in their immunogenetic backgrounds [17]. A lack of homozygosity or the shared epitope in GCA has been reported. This contrasts with observations in RA, in which homozygosity of the shared epitope is associated with a more severe disease. The particular genetic locus in PMR/GCA has been mapped to the second hypervariable region (HVR2) of the HLA-DRB1 molecule (sequence motif spanning the amino acid positions 28–31—DRYF). This HVR2 encodes sequences in the antigen-binding site of the floor of the HLA-DR molecule. However, this initial observation has not been confirmed in other populations from Europe [12, 13, 17].

Results of the study in the Slovak population confirmed a dominant role of HLA-DR4 (DRB1*04) in the predisposition to RA and GCA [18]. A significantly increased frequency of the HLA-DR4 antigen was found in GCA (58%) compared with controls (21%, $p < 0.01$). The highest frequency of HLA-DR4 was observed in GCA patients with PMR (75%). HLA-DR4 was not associated with ESR, platelet count, alkaline phosphatase and visual symptoms in GCA. The relationship with DR4 was stronger in GCA (the relative risk RR = 5) than in RA (RR = 3). A more frequent occurrence of the HLA-DR4 antigen was observed in PMR (42%), but this difference was not significant ($p > 0.05$). The association with the HLA-DR1 antigen typical for Slovak RA patients [5] was not found in GCA and PMR. RA, GCA and probably also PMR are associated with the antigen HLA-DR4 in the Slovak population. Different alleles of DRB1*04 or epitopes of the molecule HLA-DR4 can probably participate on the predisposition to RA and PMR/GCA.

During the last decade, genetic association studies have described several genes that are associated with predisposition to GCA, including genes of the human leukocyte antigen class I and II regions. The HLA-DRB1*04 alleles seem to be the most consistently associated genetic risk factors for this form of vasculitis [19]. An association between HLADRB1* 04 alleles that carry the shared epitope (SE) and GCA has been also described, which suggests common pathological mechanisms between GCA and RA [20]. Carmona et al. [21] realised a large-scale genetic

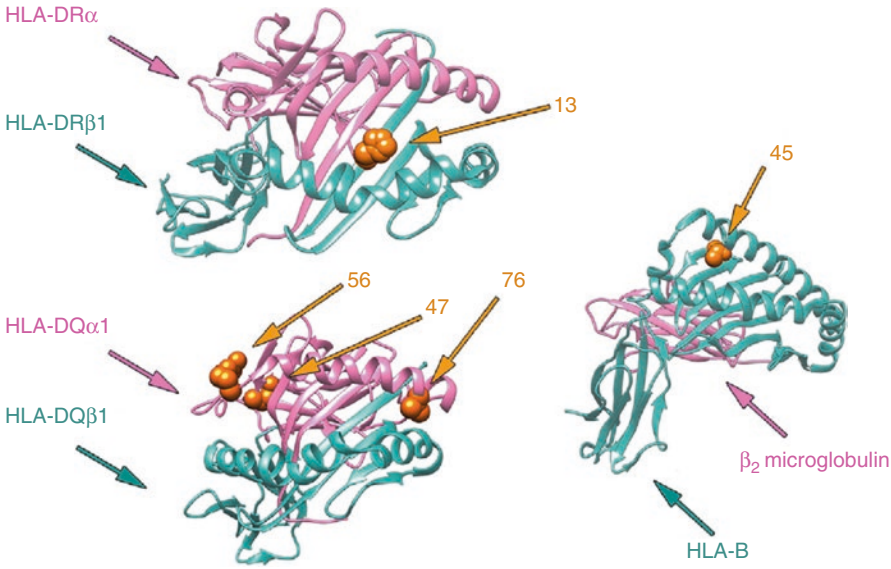

Fig. 6.1 Ribbon representation of the HLA molecules HLA-DR, HLA-DQ and HLA-B/β2 microglobulin. The amino acid positions of the HLA model associated with GCA are highlighted in orange (Carmona et al. [21])

analysis on GCA. A case-control cohort, comprising 1651 case subjects with GCA and 15,306 unrelated control subjects from six different countries of European ancestry, was genotyped by the Immunochip array. They also imputed HLA data with a previously validated imputation method to perform a more comprehensive analysis of this genomic region. The strongest association signals were observed in the HLA region, with SNP polymorphism rs477515 representing the highest peak ($p = 4.05 \times 10^{-40}$, OR = 1.73). A multivariate model including class II amino acids of HLA-DRβ1 and HLA-DQα1 and one class I amino acid of HLA-B explained most of the HLA associations with GCA, consistent with previously reported associations of classical HLA alleles like HLA-DRB1*04. An omnibus test on polymorphic amino acid positions highlighted DRβ1 13 and HLA-DQα1 47, 56 and 76 as relevant positions for disease susceptibility (Fig. 6.1). This study provides evidence of a strong contribution of HLA class I and II molecules to susceptibility to GCA [21].

Many genetic studies on GCA have been performed during recent years, making this disease the best example of vasculitis in which a genetic influence has been implicated in both disease susceptibility and severity [22]. The significant associations of non-HLA loci with GCA predisposition were observed. These mainly include genes of the immune system, the inflammatory process and the endothelial function, which are in most cases common susceptibility genes for

other vasculitides. The following brief overview presents significant associations of non-HLA loci with GCA which have been observed (adapted from Carmona et al. [19]).

6.1 Tumour Necrosis Factor (TNF)

The TNF gene, located within the MHC class III, encodes a pro-inflammatory cytokine involved in the regulation of immune cells. Elevated levels of TNF have been detected in GCA patients with a strong systemic inflammatory response, and a high production of this cytokine was associated with longer corticosteroid requirements for these patients [23]. A study of Mattey et al. [24] evidenced differential TNF microsatellite associations for GCA and PMR. TNFa2 was strongly associated with isolated GCA without PMR, and this association was independent of those for HLADRB1* 0401 and HLA-DRB1*0101. On the other hand, the analysis of patients with isolated PMR showed a statistically significant association with TNFb3, also independent of the described HLA associations HLA-DRB1*13 and HLA-DR1*14.

6.2 IFN-γ

IFN-γ is a key cytokine in the immune system involved in the innate and adaptive immunity. High expression of IFN-γ is directly related to the pathogenic mechanisms affecting the arterial walls in GCA patients [25, 26]. It has been observed that IFN-γ is released in the vasculitic lesions even after months of corticosteroid therapy [19]. Allele*3 of the microsatellite dinucleotide (CA) repeat within the first intron of the IFN-γ gene was associated with visual ischaemic manifestations in GCA patients [27]. However, no association with the global disease was observed in a subsequent study in which three different tag single-nucleotide polymorphisms (SNPs) of the IFN-γ locus were analysed, suggesting that IFN-γ functional variants may influence disease severity rather than susceptibility [28].

6.3 IL-10

IL-10 is an anti-inflammatory Th2 cytokine with pleiotropic effects in the immune system. Different functionally relevant IL-10 genetic variants have been tested for association with GCA predispositions. Two independent studies in Italian and Spanish populations indicated that variation of the IL-10 promoter region is involved in the genetic susceptibility to GCA [29, 30]. However, different association signals were observed, when the allelic frequencies between cases and controls were compared in each study. The IL-10 rs1800872 polymorphism was associated with GCA risk in the Italian population [29], whereas in the Spanish study, the associated variant was IL-10 rs1800896 [30]. Further studies in additional populations may help to narrow the IL-10 association with GCA.

6.4 IL-4

The IL-4 gene encodes a cytokine that acts reciprocally with IFN-g. Different IL-4 genetic variants showed an association with a predisposition to develop GCA, and these associations substantially increased their statistical significance when the HLA-DRB1*04 status was considered, suggesting a possible interaction between both loci [28].

6.5 IL-6

IL-6 is a cytokine with a pleiotropic effect in both the innate and adaptive immunity. A promoter polymorphism at the position 174 (rs1800795* G/C) of this gene has been shown to influence IL-6 levels and dysregulated IL-6 expression. Two independent studies performed in Italy and Spain did not report evidence of an association between the promoter polymorphism rs1800795 and predisposition to GCA [31, 32]. However, a recent report on an independent Spanish cohort identified two different IL-6 genetic variants associated with GCA (rs1546762, located in the promoter region, and rs7805828, located upstream of the 30 end of the gene) [33].

6.6 IL-18

IL-18, also known as IFN-g-inducing factor, is a pro-inflammatory cytokine. Increased IL-18 expression levels were detected in temporal artery biopsies of GCA patients [34]. The previous SNP and IL-18 rs1946518*G/T have been recently associated with GCA susceptibility [35].

6.7 Monocyte Chemotactic Protein-1

Monocyte chemotactic protein-1 (MCP-1) is a member of the CC subfamily of chemokines. An increased of MCP-1 expression was observed in patients with GCA and other autoimmune diseases, including RA and atherosclerosis [36–38]. Significant differences in the frequency of a haplotype composed of three SNPs located in intron 1, exon 2 and the 30UTR region of the gene were observed between northwestern Spanish patients and controls [39]. Evidence of an association between the MCP-1 SNP rs1860190*A/T and GCA in an independent Spanish population has been also reported [33].

6.8 Chemokine (C-C Motif) Ligand 5 (CCL5)

CCL5 gene encodes a potent chemotactic factor. Increased serum levels of this chemokine were reported in untreated PMR patients [40]. A study on GCA patients from Spain (a promoter polymorphism at position 403 rs2107538*G/A) did not

confirm statistically significant differences in the allele frequencies in GCA, but an association with the isolated PMR condition was shown [41].

6.9 IL-12 Receptor Beta 2

IL-12 receptor beta 2 (IL-12RB2) is a subunit of the IL-12 receptor whose expression is regulated by IFN-γ. A significant association between the IL-12RB2 polymorphism rs3790567*A/G and GCA susceptibility was observed, particularly with the subgroup of Spanish patients showing visual ischaemic complications [42].

6.10 Intercellular Adhesion Molecule 1

Intercellular adhesion molecule 1 (ICAM-1) encodes a cell surface glycoprotein with an important role in the interactions between immune and endothelial cells during the inflammation process [43, 44]. ICAM-1 serum levels were correlated with disease activity in GCA patients, and elevated expression of this molecule was also detected in shoulder synovial membrane of active PMR as well as in the inflammatory infiltrates of the temporal artery in GCA, which suggests that this protein may be a relevant component of the inflammatory processes of these conditions [45, 46].

6.11 Vascular Endothelial Growth Factor (VEGF)

VEGF is a key proangiogenic mediator that induces adhesion molecules on endothelial cells during inflammation [47]. Increased levels of circulating VEGF have been detected in PMR patients [48], and recent evidence suggests that these high-soluble VEGF concentrations may be related to optic nerve ischaemia in GCA patients [49].

6.12 Endothelial Nitric Oxide Synthases 2 and 3

Nitric oxide synthases (NOSs) are a family of enzymes that produce nitric oxide (NO), which is involved in a wide variety of biological processes. Three different genes encode NOSs in humans: the neuronal (NOS1), the cytokine-inducible (NOS2A) and the endothelial (NOS3) [50]. Regarding NOS2A, a TAAA repeat polymorphism within the NOS2A promoter was associated with GCA in a cohort from north-west Spain [51]. Recent evidence has confirmed that genetic variation within this locus may also be crucial in GCA predisposition, since another NOS2A promoter variant, rs2779251*A/G, showed a strongly significant protective effect for GCA [33]. Consequently, it is possible that malfunction of the NO system

could be involved in the vascular damage of GCA. Indeed, studies on Italian and Spanish populations confirmed NOS3 as a GCA susceptibility gene [52, 53]. Hence, although further studies are needed to confirm it, it is possible that these susceptibility variants may be influencing the disease phenotype by generating oxidative stress.

6.13 Matrix Metallopeptidase 9

Proteins of the MMP family are zinc-dependent enzymes with proteolytic activity on the extracellular matrix that are involved in many physiological and pathological processes [54]. An elevated expression of MMP9 has been detected in GCA lesions [55–58], and this metalloproteinase has been correlated with the progression of inflammatory infiltrates and vessel destruction and repair in GCA [59]. Statistically significant differences between the allele frequencies of GCA cases and controls were found for another non-synonymous coding MMP9 variant (rs2250889*C/G) [60].

6.14 Toll-Like Receptor 4

The Toll-like receptor (TLR) family composes a group of transmembrane proteins expressed by various cell types, including immune cells. One member of this family is TLR-4, which has been implicated in signal transduction events induced by lipopolysaccharide from gram-negative bacteria. A significant association between the non-synonymous TLR4 polymorphism rs4986790*A/G (Asp299Gly) and GCA in a good-sized Spanish cohort suggested that this gene may play an important role in GCA pathophysiology [61]. Although this association was not confirmed in two subsequent studies on independent Caucasian populations [62, 63], a trend of association was evident when the three studies were meta-analysed (p = 0.082, OR = 1.46) [64].

6.15 Fc-g Receptors

Fc receptors are cell surface proteins of the immunoglobulin superfamily that are located in the membrane of some immune cells, such as B cells, NK cells and macrophages. Those that bind immunoglobulin G (IgG) antibodies or IgG-containing immune complexes. Different polymorphisms of the FCGR genes FCGR2A, FCGR3A, FCGR3B and FCGR2B were analysed in a case-control study of a small Spanish cohort. The authors described significant associations with GCA for FCGR2A rs1801274*G homozygosity (FCGR2A-131RR) and carriage of FCGR3A rs396991*T (FCGR3A-158F). The haplotype rs1801274*G-rs396991*T (FCGR2A 131R-FCGR3A 158F) was associated with an almost threefold increased GCA risk [65].

6.16 Myeloperoxidase

MPO is a haemoprotein that is abundantly expressed in neutrophils and monocytes and secreted during their activation [66]. There is evidence suggesting that increased serum MPO levels may represent a risk marker for atherosclerosis and coronary artery disease [67, 68]. The MPO promoter polymorphism rs2333227*G/A, which affects MPO expression [69, 70], was associated with GCA predisposition [71]. It is likely that MPO represents a key component in vascular inflammatory diseases, providing a mechanism to endothelial dysfunction and vessel wall damage.

An application of the new technology genome-wide association studies helps to better understand the genetic component of GCA. Cameron et al. [21] conducted a large-scale genetic analysis on GCA. A case-control cohort, comprising 1651 case subjects with GCA and 15,306 unrelated control subjects from six different countries of European ancestry, was genotyped by the Immunochip array. The Immunochip allows a dense analysis of 196,524 SNPs, rare variants and insertion/deletion polymorphisms, located within 186 known susceptibility loci for autoimmune and inflammatory disorders [72]. The use of the Immunochip has substantially increased the number of established genetic risk factors. Two genetic variants of the protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene represented the highest non-HLA association signal with GCA (rs6679677, $p = 1.31 \times 10^{-6}$, OR = 1.39; rs2476601, $p = 1.73 \times 10^{-6}$, OR = 1.38). One of them (rs2476601) is a non-synonymous (p.Arg620Trp) functional variant that has been associated with a variety of immune-mediated diseases including GCA [38, 39]. Suggestive association ($p < 10^{-4}$) was also found for another two tightly linked SNPs located in the leucine-rich repeat containing 32 (LRRC32) region (rs10160518, $p = 4.39 \times 10^{-6}$, OR = 1.20; rs2155219, $p = 6.19 \times 10^{-6}$, OR = 1.19). Other suggestive signals included SNPs of key immune-related genes such as v-rel avian reticuloendotheliosis viral oncogene homolog (REL; rs115674477, $p = 1.10 \times 10^{-5}$, OR = 1.63), protein kinase C theta (PRKCQ; rs587198, $p = 5.72 \times 10\text{-}^{5}$, OR = 1.17), cluster domain 226 (CD226; rs1788110, $p = 6.51 \times 10^{-5}$, OR = 0.85) and NLR family pyrin domain containing 6 (NLRP6; rs3817637, $p = 8.67 \times 10^{-5}$, OR = 0.77). Similar results were observed when the dataset was analysed with inverse variance-weighted meta-analysis. However, in this analysis, REL rs115674477 corresponded with the second top signal, with a statistical significance ($p = 3.56 \times 10^{-6}$, OR = 1.67) very similar to that observed for PTPN22. In order to conduct a more detailed analysis of the top signals, authors obtained imputed data of the PTPN22, LRRC32 and REL genomic regions. A total of 922 SNPs in the PTPN22 region, 462 in the LRRC32 region and 1158 in the REL region were included in the imputed datasets. However, because of the dense coverage of the fine-mapped loci in the Immunochip, all the imputed variants showed a lower statistical significance than PTPN22 rs2476601, LRRC32 rs10160518 and REL rs115674477, consistent with previous studies [73]. The statistical significance of genes reported to be associated with GCA in candidate gene studies was checked [19]. Although the signals were relatively weak, associations at $p < 0.05$ were observed in most cases, e.g., inducible nitric oxide synthase 2 (NOS2; rs2274894), interleukin 6 (IL-6; rs10242595), IL-4 (rs2243200),

interferon gamma (IFNG; rs2193046) and IL-10 (rs74148796). The presented study confirmed a key role for the functional PTPN22 rs2476601 variant and proposed other putative risk loci for GCA involved in Th1, Th17 and Treg cell function [21].

GCA shows a complex aetiology in which both environmental and genetic factors seem to influence the development and progression of the disease. Some studies suggest that disease may be activated by environmental infectious factors or autoantigens [74]. For example, an increase in the incidence of GCA has been correlated with epidemics of *Mycoplasma pneumoniae*, *parvovirus B19* and *Chlamydia pneumoniae* in Denmark [75]. Nevertheless, there is no consistent evidence of any particular microorganism as a direct trigger factor for GCA.

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Chronobiology of Polymyalgia Rheumatica and Giant Cell Arteritis

7

Howard Bird

7.1 Introduction

Chronobiology, which is the study of biological rhythms, is perhaps unduly neglected within medicine. It assumes particular importance for diseases, many of them rheumatic diseases and polymyalgia rheumatica (PMR) in particular, where there is clear evidence of a diurnal variation in symptoms. The dramatic improvement in early morning stiffness such that it is invariably abolished by lunchtime even figures in diagnostic criteria sets for PMR.

Current thinking suggests that the diurnal variation in endogenous cortisol has evolved for the more efficient functioning of the human body during daylight hours and that this is probably mediated through other neuronal and hormonal pathways, with melatonin (MLT) a prime candidate. Such pathways are closely linked with diurnal variation in cytokines, which probably largely accounts for diurnal symptomology in rheumatic diseases since, as a group, these inflammatory conditions are cytokine driven.

In addition to influencing symptoms, diurnal rhythms have important implications for dosing, not just of non-steroidal anti-inflammatory drugs (NSAIDs) but particularly for the dosing of steroids, which at present remains the backbone of treatment in this condition.

The literature also contains reference to a seasonal variation in the incidence of PMR, though this is harder to study because of confounding factors such as the seasonal availability of health care in certain developed countries.

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7.2 Other Rheumatic Conditions

Circadian rhythms have long been recognised in rheumatoid arthritis (RA) [1]. In this condition, pain and stiffness become clinically more apparent overnight such that they are maximum at about 05.00 h, reducing gradually thereafter during the next day. This has implications both for function (e.g. grip strength) and in discomfort and disability [2]. Circadian rhythms have also been identified in other rheumatic diseases, including polymyositis, which is associated with a circadian variation in serum myoglobin levels [3].

The way in which this links with hormones has been discussed for some 20 years [4, 5]. An intricate association between neuroendocrine effect, sex hormones and symptoms is accepted. In the last decade, interest has additionally centred not only on cortisol but also cytokines, particularly interleukin-6 (IL-6), which many consider to be one of the principal cytokines mediating PMR and giant cell arteritis (GCA) [6].

7.3 Mechanisms of Variation in Rheumatic Diseases

Here, the evidence, drawn largely from RA but possibly to some extent applicable to PMR, becomes a little confusing. It is no surprise that in RA circadian variation in grip strength differs in phase by about 12 h from circadian variation in inflammation, grip strength strongest towards the late afternoon. The circaseptan rhythm (about 7 days) of paw oedema observed in animal models [7] probably lacks relevance however.

Endogenous corticosteroids and MLT are both undoubtedly implicated. In adult primates, visible light, observed by the subject, influences the hypothalamic region of the brain that directs circadian rhythms. Deprivation of observed light modifies the circadian rhythm for many neurohormones, particularly cortisol and MLT. In normal subjects, MLT peaks at about 03.00 h, whereas cortisol peaks at 04.00 h. Interleukins tend also to peak overnight and then remain low throughout the day. There also seems to be a differential effect in interleukins, overnight variation in IL-6 and cortisol both more marked than variation in TNFa or other cytokines [6].

In RA an early surge in plasma ACTH correlates closely with increased IL-6 [8], and Th-1 type cytokine also increases significantly with a peak that is even slightly earlier [1].

MLT serum levels are significantly higher in patients with RA than in controls [9], and there is even a suggestion of variation in the diurnal rhythm across Europe. Thus, when IL-6 and TNFa concentrations were observed in RA in patients from Estonia and Italy at 04.00 h and midnight, Estonian patients displayed higher cytokine levels than Italian patients, implying latitude may have an influence though this is not necessarily the only explanation for the higher prevalence in RA in northern Europe than in Mediterranean countries. The higher prevalence of PMR in Scandinavia, sometimes alternatively attributed to either genetic clustering or local infection, comes to mind.

7.4 Diurnal Variation in Polymyalgia Rheumatica/Giant Cell Arteritis

The presence of severe early morning stiffness figures prominently in several diagnostic criteria sets [10–12] as well as in the recently proposed disease activity score for monitoring response to treatment [13].

Studies on cytokine and steroid levels in PMR have been justified largely because of diagnostic confusion between PMR and elderly-onset RA (EORA). In a study of PMR, EORA and a third group of patients felt to represent EORA with a specific PMR-like onset, TNFa, IL-6, IL-1 receptor antagonist levels and steroid levels were compared together with levels in a group of control patients [14]. Serum IL-6 was significantly higher in both PMR and EORA/PMR than in EORA or control, whereas IL-1 receptor antagonist serum levels were significantly higher in patients with EORA than in controls and levels highest in patients with PMR and EORA/PMR. After glucocorticoid treatment, serum TNFa and IL-6 levels significantly decreased in all patient groups. It was argued that patients with PMR and with EORA/PMR have a more intense inflammatory reaction and might be more efficient responders to glucocorticoid treatment than patients with EORA, though a group of patients with classical RA alone was not included in this study.

In PMR, serum prolactin has been shown to be positively correlated with a variety of typical symptoms but not to correlate with typical inflammatory markers, such as ESR, CRP, IL-2, IL-6 and TNFa [15].

It remains uncertain whether the seasonal pattern in the onset of PMR reflects a function of chronobiology or has an alternative explanation. In a study from Italy [16], a winter peak of incidence was once again identified, perhaps suggesting an infective aetiology at that time of year.

7.5 Implication for Steroid Therapy

Against the above biological background, there has been recent intense interest in the most rational method of delivering glucocorticosteroid therapy. A workshop under the auspices of the EULAR Standing Committee on International Clinical Studies had first addressed this as early as in 2002 [17]. This considered not only pharmacological variation between the different steroid analogues available commercially [18] (though in practice prednisolone is invariably used by the oral route of administration) but also considered timing of dosing in relation to the circadian rhythm of endogenous cortisol production and in the diurnal variation of symptoms. It considered frequency of dosing during the day, though did not specifically consider PMR. It also accepted that answers derived from consensus conferences were not definitive. It was noted, however, that in view of the relative hypocortisolism that occurs in PMR, glucocorticoid treatment might be as much replacement therapy for reduced adrenal production as supplementary therapy [19]. Although this work was largely directed at RA, it may still have implications for PMR.

Consideration should also be given to the precise formulation of the administrated steroid and its reliability of release. There is an anecdotal impression that release from enteric-coated formulations of prednisolone is unreliable and erratic compared to non-enteric formulations. Some patients not responding to enteric-coated prednisolone respond immediately when non-enteric-coated prednisolone is substituted at the same dose. Against this background, there is evidence that in RA low doses of prednisolone taken at 02.00 h have more effect on severe morning symptoms than when the same dose is taken at 07.30 h, which might be expected, although the required awakening in the middle of the night may itself influence diurnal control. Alternative slow-release preparations, seemingly reliable, if taken at bedtime in RA release the drug automatically around 02.00 h with corresponding improvement on morning stiffness [20]. Use of this formulation in PMR has been recommended [21].

Recently Kirwan's group has studied the effects of night-time and morning administration of glucocorticoids on circadian variation of IL-6 in a small pilot study [22]. IL-6 followed a circadian variation with a peak at 04.00 h. Seven mg/day of conventional prednisone taken in the morning caused less reduction of IL-6 and area under the curve than 7 mg modified (sustained) release prednisone taken at night. Further study of sustained release preparations would now seem justified.

Treatment with alternate-day steroids has been proposed to reduce the risk of adverse reactions but has been associated with a higher dose of treatment failure [23].

Although NSAIDs are felt by the majority not to have a place in the management of PMR, it has been known for many years that a fourfold improvement in tolerance and a doubling of analgesic effectiveness can accrue as a result of varying the ingestion time of indomethacin [24].

7.6 2015 Recommendations for the Management of Polymyalgia Rheumatica

Recently an international study group representing both the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) has made recommendations for the management of polymyalgia rheumatica [25].

Evidence based, this enumerated eight overarching principles and nine specific recommendations. Recommendations in respect of prednisone dosage simply specified the minimum effective dose in the range 12.5–25 mg/day with tapering of the dose as soon as the clinical response allowed this.

A single dose rather than divided daily doses of an oral glucocorticoid was preferred except for special situations amongst which severe night pain was cited. It was argued, based on evidence from 1964, evening doses could cause circadian rhythm and sleep disturbances [26].

The panel conditionally recommended intramuscular methylprednisolone as an alternative to oral glucocorticoids and conditionally recommended the consideration of the early introduction of methotrexate.

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Neuroendocrine Changes in PMR and GCA

8

Richard Imrich and Jozef Rovenský

8.1 Summary

Polymyalgia rheumatica (PMR) and giant cell or temporal arteritis (TA) are related chronic inflammatory conditions which typically affect elderly. Age-related changes in the neuroendocrine system could also represent a pathogenic factor in genetically disposed individuals. Complex bidirectional neuroendocrine-immune relations are further modified by ongoing chronic inflammation. Good clinical response to glucocorticoids in PMR patients supports the assumption that cortisol levels are lower than would be expected during ongoing inflammation. Moreover decreased adrenal androgens levels have been observed in PMR. Possible adrenal androgens supplementation during glucocorticoid treatment sketches the new prospects in therapy of PMR and TA.

8.2 Aging and Endocrine Factors in the Pathogenesis of PMR and TA

The onset of PMR at virtually the age of 50+ as well as the further increase in the incidence with the increasing age suggest that aging may have a certain share in the pathogenesis of the disease. The concentrations of many hormones are known to

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undergo changes with the increasing age. As an example, we may mention androgens dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione (ASD) produced in the adrenals. Daynes et al. [1] and later on Straub et al. [2] had demonstrated in mice and humans, respectively, that natural aging accompanied with reduction of DHEA and DHEAS concentrations is associated with increases of pro-inflammatory cytokines such as TNF and IL-6.

The possible association between the reduction of adrenal androgens and increase in pro-inflammatory cytokines is also suggested by the fact that in vitro, DHEA is able to inhibit IL-6 secretion in cultured human mononuclear cells [2, 3]. DHEA at the same time is able to influence differentiation of T_H lymphocytes and thus the direction of the immune response between T_H1 and T_H2 lymphocytes. Any disbalance between factors influencing differentiation of T_H1 and T_H2 lymphocytes could play a role in the maintenance of chronic inflammation [4, 5]. The natural reduction of the concentrations of adrenal androgens associated with an increase in the concentrations of pro-inflammatory IL-6 at older age might thus predispose to the development of PMR and TA.

8.3 Function of the Hypothalamus-Pituitary-Adrenal (HPA) Axis in PMR and TA

Genetically determined disturbances of the HPA axis may play a role in enhanced susceptibility to PMR and TA. Gonzalez-Gay et al. [6] studied polymorphisms of the promotor region of the CRH gene. However, they could not find any association with increased susceptibility to PMR or TA. TA patients, carriers of the CRH-A2 allele, however showed higher frequencies of ophthalmologic complications.

Measurements of the concentrations of adrenal hormones in patients with recent onset of PMR prior to the initiation of glucocorticoid therapy and their comparison with the levels measured for age- and sex-matched healthy controls showed lower DHEAS concentrations in the former. A similar decrease of DHEAS concentrations was observed in also TA and other chronic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus [7, 8].

Contrary to DHEAS, cortisol concentrations in patients at the time of the PMR diagnosis did however not significantly differ from those in healthy controls. An intricate feedback system probably maintains cortisol levels within the normal range. Because of the ongoing inflammation however cortisol secretion remains insufficient [3]. Also, a very good therapeutical response to the administration of exogenous glucocorticoids suggests that there might be a relative deficit of the endogenous hormones.

In another study, dynamic tests (corticoliberin and adrenocorticotropic hormone stimulation) were used to evaluate the functional status of the HPA axis in PMR prior to the initiation of the glucocorticoid therapy. No significant difference in the response of the adrenocorticotropic hormone (ACTH) or cortisol could be established as compared to healthy controls, comparable ACTH concentrations however resulted in a pronouncedly higher secretion of 17-hydroxyprogesterone that is a

cortisol precursor, and ASD during steroidogenesis in the adrenals [9]. Changes in steroidogenesis in terms of DHEAS reduction, relative cortisol deficit accompanied by the accumulation of the precursor of the latter, could represent additional factors of the pathogenesis of PMR and TA.

8.4 Reasons for Disturbed Steroidogenesis

Cutolo et al. [9] believe that disturbances in glucocorticoid biosynthesis could be associated with altered activity of 21-hydroxylase that catalyzes the conversion of 17-hydroxyprogesterone to 11-deoxycortisol. Although inhibiting expression of 21-hydroxylase in cultured human fetal adrenal cells [10], TNF is not likely to play a significant role in the pathogenesis of PMR [11].

TNF and IL-1 inhibit in vitro activity of the enzyme P450c17 (17-alpha-hydroxylase with 17,20-lyase activity), upon which, among others, also DHEA and thus DHEAS synthesis are dependent [10]. No increased concentrations could however be observed in PMR patients compared to age-matched healthy individuals. As already mentioned, TNF and IL-6 concentrations increase during the natural aging process. DHEAS deficit during the aging could thus be a result of the changes in the activity of 17-alpha-hydroxylase.

IL-6 whose concentrations are markedly increased in both PMR and TA however does not markedly influence 17-alpha-hydroxylase or 21-hydroxylase activities in adrenal cells in vitro [11]. As before, the issue of specific reasons for the altered steroidogenesis in these diseases thus remains not well understood.

8.5 IL-6 and Its Further Effects on the HPA Axis

Effects of inflammatory mediators get however manifested on also other levels of the HPA axis. Upon administration, exogenous IL-6 is able to stimulate CRH secretion at the hypothalamic level, of ACTH in the pituitary, and to affect the activity of enzymes involved in steroidogenesis in the adrenals [12]. As a result of the release from the site of inflammation during the acute stage of inflammation cytokines such as IL-1 beta, IL-6 and TNF trigger release of the hormones which are able to modulate in turn the activity of the inflammatory process. Adaptation changes of the HPA axis to chronic stimulation by inflammatory cytokines however result, over time, in suppression as suggested, e.g., by the therapeutical use of IL-6 in tumor treatment or posttraumatic conditions. The development of subsequent adaptation changes of the HPA axis could be a result of an enhanced endogenous cortisol secretion and/or of a direct action of IL-6 [3].

Under normal conditions, ACTH secretion stimulated by acute inflammation results in elevations in the concentrations of all the three adrenal hormones—cortisol, ASD, and DHEAS. Consequently, the question arises whether immunosuppression of chronic inflammatory diseases by glucocorticoids should not be accompanied by adequate supplementation with DHEA or ASD [3].

8.6 Cytokines in Polymyalgia Rheumatica and Giant Cell Arteritis

Cytokines play an important role in the regulation of immune responses. Markedly elevated interleukin 6 (IL-6) and IL-1 receptor antagonist concentrations were found at the time of PMR diagnosis, thus prior to start of glucocorticoid therapy. On the other hand, systemic concentrations of other anti-inflammatory cytokines, such as tumor necrosis factor (TNF) and IL-1 beta, were comparable with those measured in healthy controls [13].

Biopsy samples of temporal arteries showed mononuclear cell, T-cell and macrophage infiltration in the vascular wall, and disturbed lamina elastica of the temporal artery. IgG, IgM, and IgA; complement; and fibrinogen deposits were identified in the lesions. Moreover, enhanced IL-1 beta and interferon (IFN) gamma production and slightly reduced production of TNF were identified [14]. IFN gamma seems to be an important factor, which modulates hyperplasia of the intima in the inflammation-affected vessels [15].

Systemic concentrations of IL-6 are elevated in GCA. IL-6 in the media of vessels is mainly produced by macrophages, whereas it is also produced by fibroblasts in the intima. Expression of the gene for IL-6 was not observed in endothelial cells or giant cells. As a result of glucocorticoid therapy, systemic concentrations of IL-6 decrease. IL-6 production in the involved arteries may thus contribute to general symptoms of GCA [16]. In GCA and PMR patients, expression of IL-6 and IL-1 beta was observed in about 60–80% circulating monocytes. It has been suggested that GCA possibly consists of two components: inflammatory reaction of the vascular wall and systemic monocyte activation, while in the case of PMR, there probably is systemic monocyte activation without vasculitis [17].

Inflammation in the portal and lobular region of the liver with focal liver cell necrosis can be observed, sometimes accompanied with the formation of small epithelioid cell granulomas. Subtle inflammatory changes may be visible in the synovial tissue: the synovial fluid shows a slight inflammatory activity.

Conclusions

- In genetically predisposed individuals, aging and the associated alterations of the endocrine and immune systems make a contribution toward the development of PMR and RA.
- Subsequent development of chronic inflammation further modifies the neuroendocrine response in the direction of insufficient secretion of cortisol and adrenal androgens.
- This assumption is supported by a good therapeutical response to exogenous glucocorticoids.
- Replacement of adrenal androgens presents new opportunities in the management of PMR and TA.

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Imaging Techniques: Positron Emission Tomography in GCA and PMR

9

Zdeněk Řehák

9.1 Positron Emission Tomography

Positron emission tomography (PET) is a diagnostic method showing general biodistribution of positron radiotracers, the most widely and routinely used of which is 2-[18F]fluoro-2-deoxy-D-glucose (FDG). FDG is a glucose analogue containing radionuclide fluorine ^{18}F, which decays by positron (β+) emission, with a half-life of 109.7 min. Diagnosis with the use of FDG-PET ("PET") combines high imaging quality (mainly sensitivity and resolution as compared to "conventional scintigraphy") and radiotracers with a favourable biodistribution and a relatively high affinity for both tumour and inflammatory cells. As a result, what is a disadvantage for oncologic imaging is a benefit for imaging of inflammations. PET scanner was adequate to provide a "functional metabolic" image of radiotracer biodistribution, however, without any anatomical-morphological information. The current hybrid PET/CT imaging systems are a combination of both methods (PET and CT), providing the respective image in the same scope and at relatively close time points. PET/CT scanners have also reduced the scanning time by about one half as compared to the initial PET scanners and increased image resolution. CT may be performed both in the low-dose (LD) and in the high-dose (HD) diagnostic mode with the possibility to use both positive and negative contrasts.

(PET/CT scanner in the HDCT mode with the use of intravenous iodinated contrast medium provides maximum diagnostic details.) Availability of the examination is relatively increasing with the growing number of PET centres.

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9.2 GCA

Patients with giant cell arteritis (GCA) may be indicated for PET (PET/CT) examination both for the purpose of initial diagnosing or monitoring of the activity of the already diagnosed disease. In the first case, it is rather a broader differential diagnostic examination within general assessment of a patient with systemic symptoms of an inflammatory condition, with laboratory evidence of active inflammation (high erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels). Such a patient is indicated for examination in order both to reveal an inflammatory condition and to rule out any occult malignancy. Studies of groups of patients examined for fever of unknown origin (FUO) or, more generally, for protracted febrile episodes report about 10–28% of patients with suspected large-vessel vasculitis [1–4]. It highly depends on the composition of the cohort and age of patients. Currently, there exist numerous studies in the literature referring to such groups of patients, with sensitivity values ranging between 77 and 92% and specificity values between 89 and 100% [5]. A typical positive PET scan in GCA patients shows tubular accumulation of radiotracer (FDG), where the arterial lumen remains free of tracer (photopenic area) and only arterial walls are "active". Examination with the use of a hybrid PET/CT scanner may show correlation also with thickening of the arterial wall, sometimes only a fine soft-tissue border in the aortic wall, although these findings may be only vague. Findings of a relatively high FDG uptake in the walls of large arteries in patients with GCA are quite uniform and may be observed in almost all sections of the aorta, with a relatively more frequent involvement of arteries originating from the aortic arch—brachiocephalic trunk, common carotid artery and subclavian artery—with continuation to brachial artery (here also symmetrical) (Fig. 9.1). High FDG accumulation is seen also in the iliac and femoral arteries. With a standard whole body protocol (skull base to mid thighs), the detection capacity of PET (as well as PET/CT) covers the area up to the neck, the carotid artery (approximately at the point of its bifurcation), the cervical part of the vertebral artery and the brachial artery in upper limbs. Meller et al. reported five patients with early aortitis; in all of them, they detected a high FDG uptake in the aortic walls and other arterial regions. High FDG uptake in these patients was found in a total of 28 vascular regions, while only nine of these regions (32%) showed vasculitis also on MRI. In other cohorts, high FDG uptake was demonstrated in the arteries that did not show the signs of involvement according to CTA or MRA [6, 7]. One of the benefits of PET or PET/CT scanning may be the fact that it detects GCA at the time when structural changes relevant for typical angiograms (CTA, MRA) have not developed yet. PET is a metabolic, functional image revealing metabolic activity of inflammation. Thus, examination makes sense only in patients prior to commencement of immunosuppressive or glucocorticoid therapy. In our view, the therapy may induce a relatively rapid decrease in the inflammation activity (and, consequently, impact visualization of FDG uptake in large arteries). There is also evidence of rapid subsidence of signs of inflammation during radiological imaging examinations, and it is recommended to perform these examinations before commencement of immunosuppressive therapy, as sensitivity (not specificity) of both

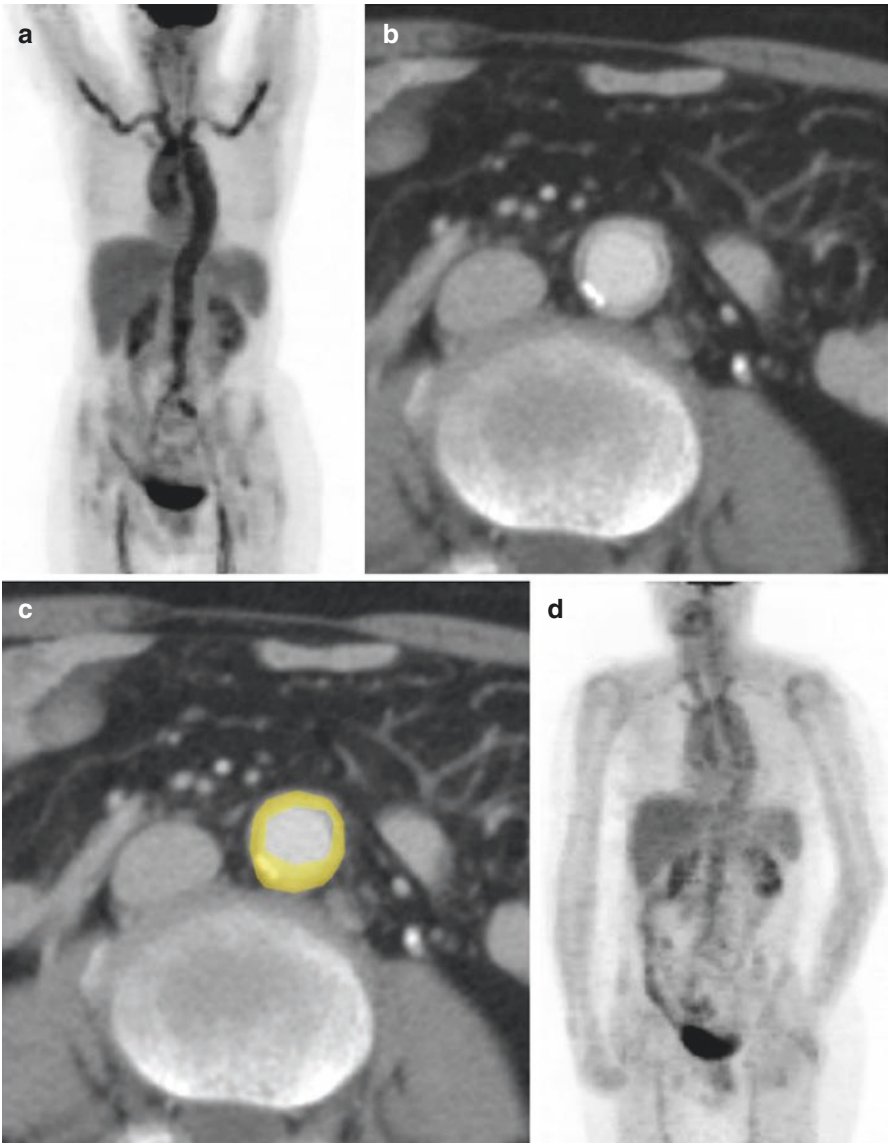

Fig. 9.1 A case study—a 66-year-old woman. (**a**) PET-MIP (maximum intensity projections, summed pseudo 3D image) of the body evidencing active vasculitis. High FDG accumulation in the aorta and large arteries exceeding the reference liver accumulation *t*. (**b**, **c**) CTA was performed due to suspected vasculitis; a fine soft-tissue border in the aortic wall correlates in fusion of both examinations with metabolically active aortic wall (*yellow ring*). (**d**) Follow-up PET examination after 7 months of glucocorticoid therapy demonstrates decrease in FDG accumulation in large arteries

US and MRI decreases from the very first day of the treatment [8]. Unfortunately, there is no information about the effect of the therapy on subsidence of signs that can be visualized by PET (PET/CT) examination. In those patients who are indicated within a broader differential diagnosis of unknown inflammatory condition for PET (PET/CT) examinations, we consider reasonable to begin with immunosuppressive therapy only after this examination in order not to distort signs of vasculitis, if present.

9.3 Monitoring of Therapy

Both PET and PET/CT examination may be used to monitor the course of the disease. Decrease in the radiotracer uptake during glucocorticoid therapy has been documented in correlation with nonspecific inflammation markers (ESR, CRP), platelet count and haemoglobin levels (inverse correlation in case of haemoglobin) [7, 9]. As early as 2006, Blockmans et al. published a study of 35 patients with GCA, in which they performed PET examination initially and 3 and 6 months after glucocorticoid therapy. Already this study has shown that PET is a sensitive marker for GCA and documented a significant decrease in metabolic activity of inflammation after 3 months of therapy that may be also quantified. At the same time, the study has demonstrated that FDG accumulation in large arteries does not further decrease after 6 months of therapy and that GCA relapses cannot be predicted by results of former PET scans (quantification in the initial study) (18 of 35 patients) [10]. PET/CT examination was also used to provide evidence of the disease persisting despite the treatment, in correlation with clinical and laboratory signs of its activity [11]. At the same time, therapeutic response to cyclophosphamide has been also assessed in patients with GCA resistance to glucocorticoids [12]. We are aware that despite a relatively sufficient evidence related to the use of PET (PET/CT) and reasonability of this examination, these methods have not become standard procedures for GCA diagnosis or monitoring yet.

It may be summarized that published studies provide a clear indication of FDG-PET and PET/CT benefits in evaluation of the diagnosis and therapy in patients with GCA, early detection, assessment of the extent of vessel inflammation and specification of the area for biopsy [10, 13, 14]. Several ways to evaluate radiotracer uptake in vessel walls have been proposed. Visual methods are more specific than semiquantitative ones, but they have lower sensitivity. The most commonly used semiquantitative method is SUVmax (maximum standardized

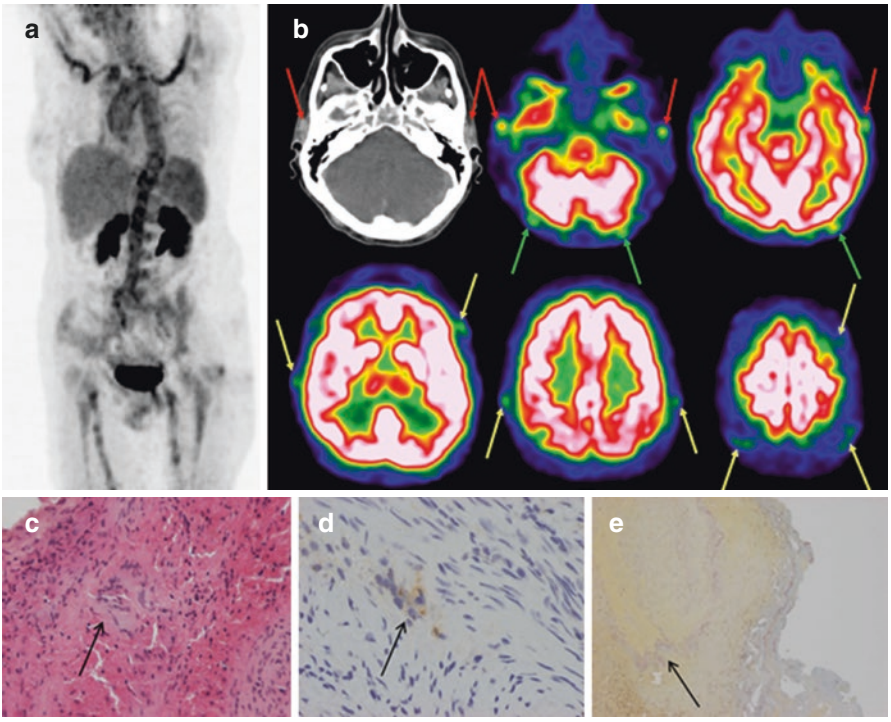

Fig. 9.2 A case study—a 63-year-old woman. (**a**) Hybrid PET/CT examination of the body (PET-MIP) revealed in the patient with fever of unknown origin a high FDG accumulation in aorta and large arteries. (**b**) Additional special brain imaging detected high FDG accumulation also in temporal arteries (*red arrows*), their frontal and parietal branches (*yellow arrows*) and occipital arteries (*green arrows*). Histological examination from excision of the left temporal artery proved giant cell arteritis. (**c**) HE, magnification 200×, stained multinucleated cells, (**d**) immunohistochemical examination—anti CD 68+, magnification 200×, stained multinucleated cells, (**e**) resorcin-fuchsin, magnification 100×, stained disintegration of the internal elastic lamina (elastica)

uptake value) aorta-to-liver ratio or aortic-to-blood pool uptake ratio [15, 16]. It seems that scanning in 180th minute as compared to standard scanning in 60th minute after the FDG application further improves detection capacity of PET/CT [17]. Addition of head imaging to the brain protocol may contribute to a better detection of inflammation in the region of temporal, vertebral and occipital arteries [18] (Fig. 9.2).

9.4 Coincidence of GCA and PMR

Experience gained in PET and PET/CT examinations also shows that the association between PMR and GCA is very close, and it may emerge as one disease with different manifestations.

Increased accumulation of FDG in the wall of an aorta including rising branches (subclavian and brachial arteries, brachiocephalic trunk and iliac and femoral arteries) is a typical sign of GCA-PET/CT scan. On the other hand, increased FDG accumulation in periarticular (around shoulders, hips and sternoclavicular joints) and extraarticular regions (in synovial structures—bursae between spinous processes in the spine or ischiogluteal bursae) is typical for PMR, including radiotracer uptake in the prepubic location (Fig. 9.3).

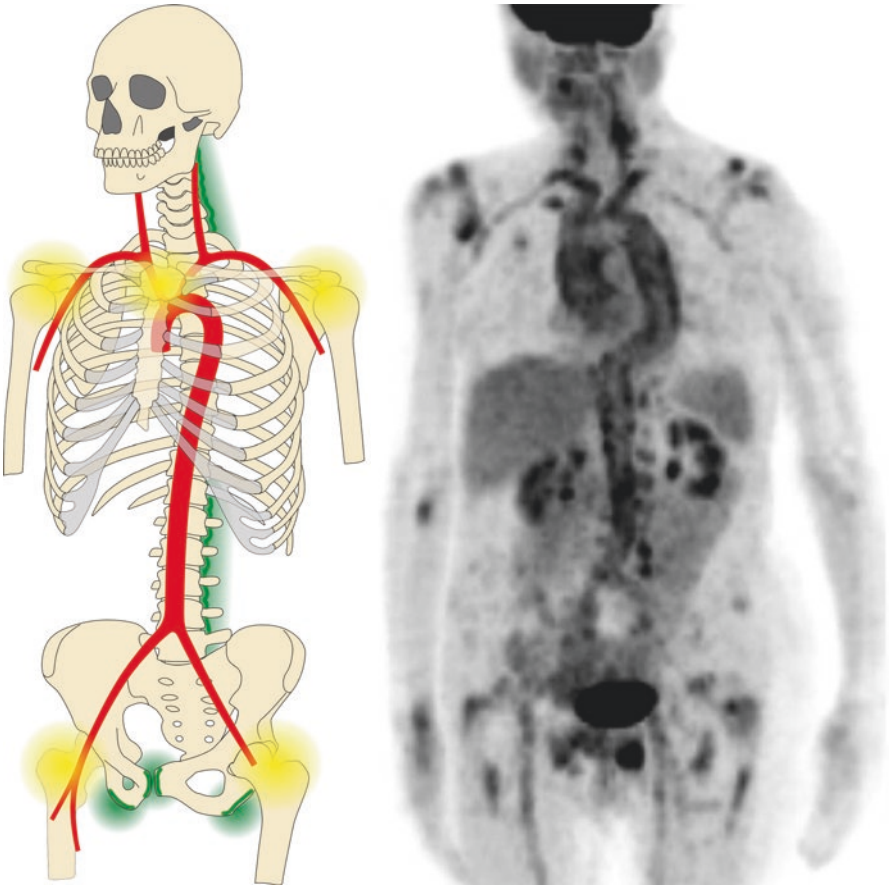

Fig. 9.3 FDG distribution in the torso of a PMR patient with developed signs of coincidental GCA. Schema (*left*) and left anterior oblique view MIP (*right*), with addition of the following colouring: (1) Articular/periarticular FDG uptake (shoulders, hips, sternoclavicular joints)—*yellow colour*. (2) Extraarticular FDG uptake (cervical and lumbar interspinous bursae, ischiogluteal bursae around ischiadic tubers) and prepubic FDG uptake—*green colour*. (3) Vascular FDG uptake (giant cell arteritis)—*red colour*. Adapted with permission of Rehak et al. [20]

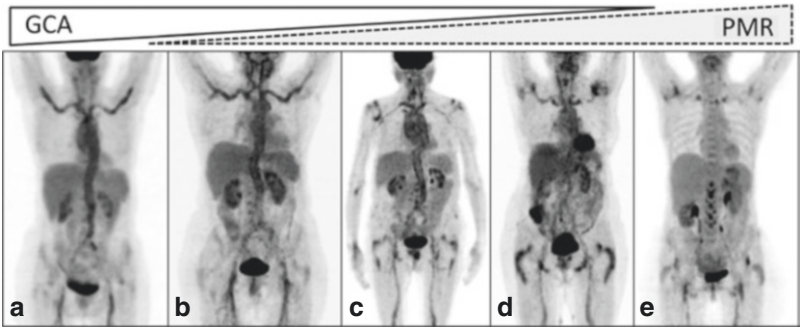

Fig. 9.4 FDG-PET/CT, MIP (maximum intensity projections)-PET scans of torso in patients with GCA and PMR. Cases **a** and **b** are typical for GCA and cases **d** and **e** are typical for PMR cases, while case **c** represents a mixture of features. Lesser mixtures of PMR and GCA signs are also seen in cases **b** and **d**, with predominance of only a subset of components. This demonstrates that the characteristic signs of GCA and PMR are frequently not clear or exact

In 2006 and 2007, Blockmans et al. published two PET studies. In the first study with 35 GCA patients, a clearly increased shoulder FDG uptake was seen in 11/35 (31.4%) patients. On FDG-PET, large-vessel vasculitis was found in 29/35 (82.9%) patients [10]. In the second study, Blockmans et al. presented FDG-PET examinations of 35 patients with PMR and detected vasculitis in only 11/35 (31.4%) patients and only in the form of a mild increase in FDG uptake; however, high FDG uptake in shoulder and hip joints was detected in almost all patients [19]. These two studies with GCA and PMR patients were the first to visualize the possible accompanying vasculitis and the association of polymyalgia rheumatica, using PET. Also in our study, large-vessel vasculitis was found in 27/67 (40.3%) patients [20]. Thus, we have arrived at a similar conclusion as Blockmans et al. (Fig. 9.4). We have also detected metachronous PET/CT presentations of active GCA and PMR. Yamashita et al. presented the case of a patient with high FDG uptake in the shoulders, near ischial tuberosities and lumbar spinous processes who was treated with nonsteroidal anti-inflammatory drugs and salazosulfapyridine (and not with corticosteroids) and who experienced remission after 6 months. Two years later after another febrile episode (with CRP and ESR elevation), high FDG uptake in large arteries was present, with isolated vasculitis but without high FDG uptake in proximal joints and in extraarticular synovial structures as seen in the preceding examination [21].

9.5 Periarticular Accumulation

Periarticular accumulations are the most common type of FDG pattern in PMR patients. In FDG-PET examinations, Blockmans et al. detected high FDG uptake in shoulders in 33/35 (94.3%) patients and in hips in 31/35 (88.6%) patients [19]. In another hybrid PET/CT study published in 2012, high FDG uptake in shoulders and hips was detected in 12/14 (85.7%) patients with relatively low specificity, 24.9% for shoulders and 64.7% for hips [22]. In our study, high articular/periarticular FDG uptake in shoulders was detected in 58/67 (86.6%) patients and in hips in 47/67(70.1%) patients [20]. Recent PET/CT studies revealed positivity in shoulders

in 16/18 (88.9%) and in hips in 17/18 (94.4%) patients and in 11/15 (73.3%) and in 11/15 (73.3%), respectively [23, 24].

It is difficult to distinguish shoulder or hip girdle synovitis and periarticular bursitis in PET or PET/CT examinations. High FDG uptake can spread from articular capsule to surrounding tissues including peribursitis locations. Nonetheless, it is possible to assess this FDG accumulation not only in shoulders and hips but also in near bursae [24, 25].

The other prominent sites exhibiting increased FDG accumulation are sternoclavicular joints, presenting positivity in 6/14 (42.8%), 31/67 (46.3%) and 13/18 (72.2%) patients, respectively [20, 22, 23].

9.6 Extraarticular Accumulation: Interspinous and Ischiogluteal Bursitis

PMR can be accompanied by extraarticular synovial involvement, i.e. as in bursitis. Blockmans et al. were first to describe high FDG uptake surrounding vertebral spinous processes of vertebrae in approximately half of their PMR patient population, 18/35 (51.4%) [19]. These observations were confirmed by other groups showing the increased FDG uptake near the cervical spinous processes in 13/67 (19.4%) patients [20] or in 10/18 (55.6%) patients [23] or uptake in lumbar spinous processes in 38/67 (56.7%) patients [20] or in 13/18 (72.2%) patients [23]. Furthermore, the radiotracer uptake was detected in intervertebral joints [24, 26].

A correlation between interspinous bursitis seen as high-contrast enhancement (MRI) and high FDG uptake (PET/CT) was published in 2012 by two author groups [22, 27]. A hypothesis of interspinous bursitis as one of the signs of PMR was evaluated using MRI on patients in 2008. In 12 patients with active PMR, bursitis in C5–C7 cervical interspinous spaces was described on MRI and was significantly more frequent in patients with PMR than in controls with various inflammatory and noninflammatory disorders [28]. Soft-tissue dense infiltration surrounding vertebral spinous processes with overlap to the subcutaneous tissue can be detected by FDG-PET/CT [20]. Other published case reports of patients examined on PET/CT scanners noted high FDG uptake in surrounding vertebral spinous processes and in other extraarticular synovial structures (bursae around ischial tuberosities and femoral trochanters). These were found either individually or in combination with proximal joint involvement or with vasculitis or in a combination of all three. For example, FDG uptake positivity was reported near ischial tuberosities in 17/18 (94.4%) patients [23], in 35/67 (52.2%) patients [20], in 12/14 (85.7%) patients [22] and in 14/15 (93.3%) patients [24].

It appears that extraarticular involvement (bursitis) detected using FDG-PET/CT might be typical for PMR patients, with reasonable sensitivity (85.7%) and

specificity (88.2%) when considering high FDG uptake in at least two of three locations (ischial tuberosities, greater trochanters, spinous processes) [22].

9.7 Extraarticular Accumulation: Enthesitis and Tenosynovitis

An infrequent sign of PMR in PET/CT is increased accumulation of FDG in front of pubic bones (Fig. 9.5) [20, 23, 24].

MRI findings of inflammation in front of the symphysis in patients with PMR were published in 2015 [29]. It is reasonable to suspect that this correlates with features of enthesitis and tenosynovitis of the pectineus muscle and adductor longus rather than bursitis.

In patients with developed signs of the disease (always with high periarticular FDG uptake near shoulders, hips and sternoclavicular joints), including high radiotracer uptake in ischiogluteal or interspinous bursae and in the prepubic region, it is sometimes possible to detect increased FDG uptake in front of the anterior inferior iliac spine. This inflammation in PMR patients related to the rectus femoris muscle confirms the pioneer observation of Wakura et al. in 2016 [24].

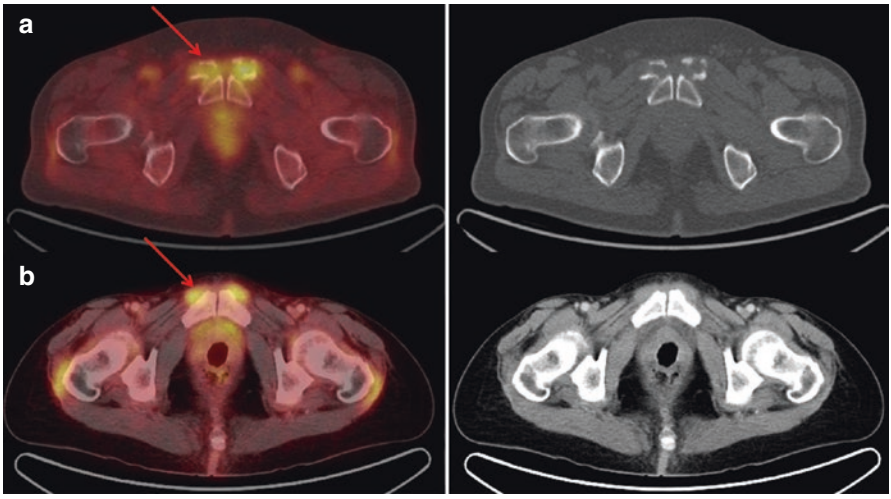

Fig. 9.5 Axial slices with a positive prepubic findings in two different patients ((**a**) a 73-year-old man, (**b**) a 54-year-old woman) detected by FDG-PET/CT. FDG uptake hot spot in the fused image (*left*, *arrow*) corresponds to metabolically active inflammation in the insertions of the muscles located in front of the symphysis (pectineus, adductor longus muscle)

9.8 Monitoring of Therapy

Decreasing FDG accumulation, as a reaction to effective treatment (corticosteroids) and in concordance with clinical and laboratory remission (decrease of ESR and CRP levels), has been documented in separate case reports and also in a cohort of patients examined using PET alone or PET/CT [19, 22, 26]. Recently, this reaction was also described in a patient undergoing therapy with the targeted monoclonal antibody tocilizumab [23]. Also, disease relapse may be mirrored by re-accumulation of FDG. This relapse is often presented as only a partially positive disease (not in all previously impaired locations) and often with sidedness asymmetry (Fig. 9.6). It may be reasonable to use FDG-PET/CT examination as follow-up monitoring, as in GCA.

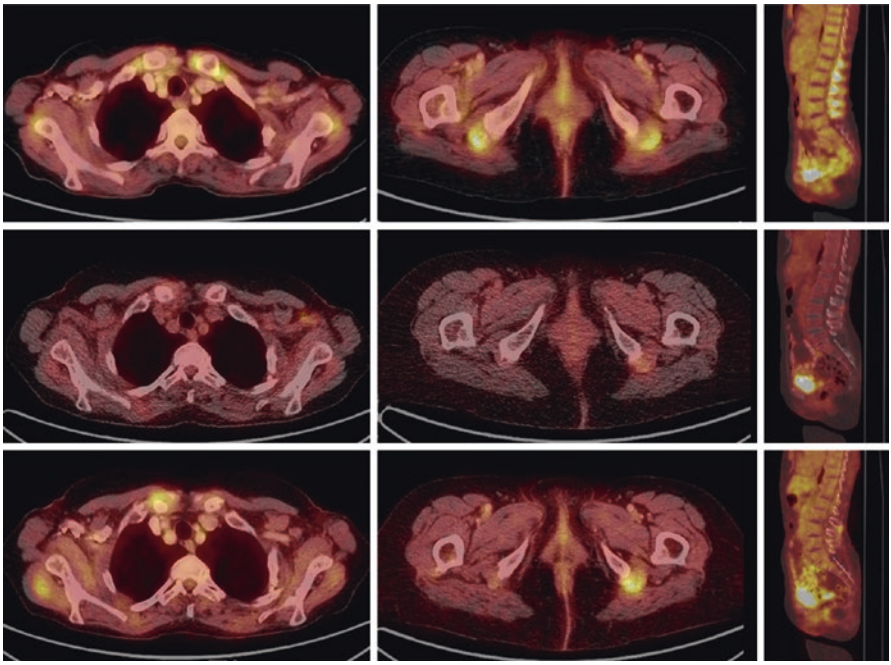

Fig. 9.6 FDG-PET/CT images of axial and sagittal slices from a unique patient. Signs of disease are present in the region of sternoclavicular joints (*left column*), ischiogluteal bursae (*middle column*) and lumbar spinous interspaces (*right column*). The upper row represents the status prior to steroid therapy and is compared with findings after therapy as presented in the middle row. The lower row demonstrates PMR relapse two years after termination of steroid therapy. Together with laboratory measurements showing the patient's increase in concentration of CRP and elevated FW, an FDG accumulation was observed around the right sternoclavicular joint, around the left ischiogluteal region and in one lumbar spinous interspace

9.9 Conclusion Concerning PMR

It is possible to use FDG-PET/CT examination in treatment-naïve PMR patients. Most commonly, periarticular signs of pathology around shoulders and hips as well as sternoclavicular joints have been reported. However, accumulation also presents exraarticularly between spinous processes in the spine, in ischial tuberosities, in the prepubic region and sometimes in unique combination. Approximately 30–40% of PMR patients present with signs of giant cell arteritis. In the regions described above, it is possible to detect a decrease or even complete disappearance of pathological FDG uptake in response to effective treatment, which can be useful for monitoring treatment as well as for detection of PMR relapse.

FDG-PET/CT examination seems to be an advantageous one-step diagnostic modality for detecting different variants of PMR involvement, for assessing extent and severity and also for excluding occult malignancy. In contrast to other imaging modalities (ultrasound and magnetic resonance imaging), PET/CT does not need targeting to a limited body part and can provide whole body examination. However, PET/CT has several disadvantages in routine examination of PMR patients: (1) high cost, (2) a worse accessibility of non-cancer slots in PET centres and (3) not inconsiderable radiation exposure.

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Usefulness of ^{18}F-FDG PET/CT for the Diagnosis of Polymyalgia Rheumatica

10

Lenka Franeková

Polymyalgia rheumatica (PMR) is a type of inflammatory rheumatologic disease manifested by myalgias in the neck, as well as both the shoulder and pelvic girdles, and morning stiffness. The disease usually affects persons over the age of 50 years. Because PMR has no specific laboratory marker (antibody), the diagnosis is based on a combination of clinical symptoms and elevated reactants of the acute phase, after other rheumatic diseases have been excluded. Diagnostic problems occur in situations where the clinical syndrome is atypical or the reactants are normal. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) may support a PMR diagnosis by determining areas of increased glucose metabolism in the surroundings of the shoulder, hip joints, and spinous processes of the vertebrae. Sensitivity and specificity of PET/CT for the diagnosis of polymyalgia rheumatica have yet to be determined. We describe a case of a patient with typical symptoms of polymyalgia rheumatica, almost normal reactants of the acute phase, and a PET/CT pattern characteristic of PMR, in order to demonstrate the special situation in which a PET/CT examination may be useful.

A 72-year-old woman was presented to the rheumatologist with myalgia and morning stiffness in the neck, shoulders, upper arms, and groin within the last 6 weeks. The erythrocyte sedimentation rate was 4 mm/h, and the C-reactive protein (CRP) was 6.2 mg/L (normal ≤5 mg/L). Muscle enzymes (creatine kinase, lactate dehydrogenase) and myoglobin were normal. No antinuclear antibodies, rheumatoid factor, citrullinated peptides, and cytoplasmic or perinuclear antineutrophilic cytoplasmic antibodies were detected. She had no symptoms and no duplex ultrasound abnormality suspecting temporal arteritis. Oncological screening was negative (normal blood count, calcaemia, serum protein electrophoresis, X-ray of the chest, abdominal ultrasound, mammography, negative fecal occult blood test).

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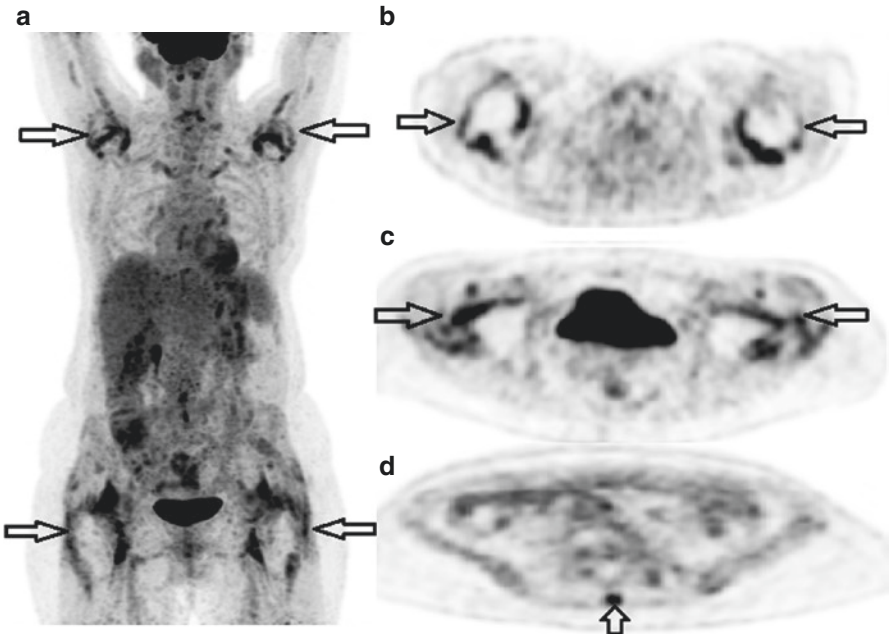

Fig. 10.1 PET scan images in a patient with polymyalgia rheumatica. (**a**) Scan showed an increased FDG uptake around the shoulders and hips. (**b**) Transversal image of the shoulders. (**c**) Transversal image of the hips. (**d**) Increased FDG uptake in the spinous process of the lumbar vertebrae (in the transversal plane)

Due to the sole marginal elevation of CRP and risk of adverse effects of corticoid therapy, we decided to perform a PET/CT examination. We found areas with inflammation around the shoulders, hips, and spinous processes of the vertebrae, supporting a diagnosis of polymyalgia rheumatica (Fig. 10.1). The diagnosis of polymyalgia rheumatica in this patient was based on a combination of typical clinical symptoms and the PET/CT findings.

In addition to these typical locations of inflammation, commonly reported in the literature in patients with PMR, we discovered on the PET/CT scan inflammation sites in the area of both ischial tuberosities (Fig. 10.2). The patient also had pain in the buttocks when sitting. Therapy with prednisolone 15 mg/day led to the rapid relief of all symptoms.

10.1 Discussion

The diagnosis of polymyalgia rheumatica is difficult, because no specific test is available for this disease. The diagnostic process begins with exclusion of infection and oncologic and other rheumatic diseases. Patients with polymyalgia rheumatica should have normal muscle enzymes and negative antibodies. The diagnostic

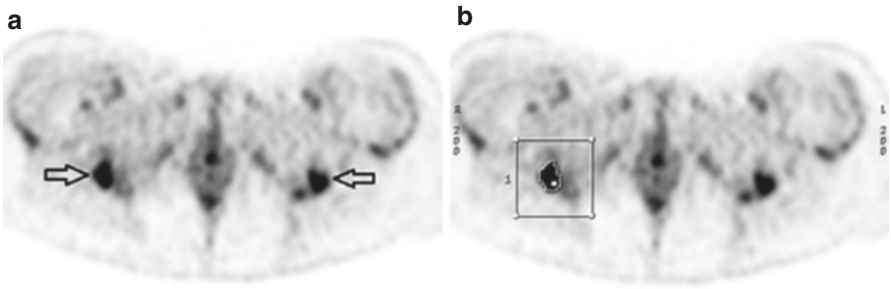

Fig. 10.2 Transversal PET scan of the pelvis on the level of the ischial tuberosities. (**a**) Scan showed an increased FDG uptake in the area of the ischial tuberosities. (**b**) Measure of FDG uptake in the ROI (region of interest) of the left ischial tuberosity: SUV (standardized uptake value) maximum 8.2 and average 3.5

criteria for PMR are based on a combination of clinical symptoms and the elevation of inflammatory parameters—erythrocyte sedimentation rate above 40 mm/h and CRP ≥ 6 mg/L [1]. However, 6% of patients with PMR show a normal sedimentation rate, and 1% of them also show normal CRP levels [2]. In these cases, diagnostic doubts arise, as well as concerns about the adverse effects of improperly administered corticoid therapy, particularly in patients with obesity, diabetes, or with depression. EULAR/ACR classification criteria for polymyalgia rheumatica are not intended to be used for determining the diagnosis but only for differentiating PMR from other rheumatic diseases such as rheumatoid arthritis [3]. These criteria also include ultrasound features of both the shoulders and hips. Considering the frequent coincidence of polymyalgia rheumatica with giant cell arteritis (GCA), its dominant symptom being the new onset of a headache (as well as visual disturbance and jaw claudication), abnormalities of the superficial temporal artery should be excluded because of a high risk of irreversible vision loss.

PET uses fluorine-18-fluorodeoxyglucose (^{18}F-FDG) to display areas with accelerated glucose metabolism and CT in order to specify their locations. Areas of inflammation, tumor, or infection are visualized using this method. In patients with PMR, areas with increased FDG accumulation have been described in the surroundings of shoulder joints, hip joints, and spinous processes of some vertebrae of the spine [4, 5]. Slightly elevated vascular accumulation (FDG uptake) at the subclavian arteries was also observed in 31% of patients with PMR [6]. MRI scans of affected joints verified the predominant presence of various types of bursitis (subacromial/subdeltoid bursitis, trochanteric bursitis) and, in 30%, also synovitis of the glenohumeral and hip joints. The occurrence of bursitis was also described in the area of the spinous processes. The inflammatory activity pattern in the area of the ischial tuberosities, such as in our reported patient, seems to be a more specific PET/CT finding for PMR than trochanteric bursitis. Only a few studies using PET/CT in PMR have been published in the literature [7]. Muscle pain and stiffness, as well as pain in the ischial tuberosities, subsided after administration of corticoid therapy.

Sensitivity and specificity of ^{18}F-FDG PET/CT features for the diagnosis of polymyalgia rheumatica have yet to be determined. PET/CT assessment is not suitable for common clinical practice due to its lower availability, radiation load to the patient, and financial costs. It can be used in cases of any diagnostic doubts, especially for the minority of patients who show no elevations of serologic inflammatory parameters.

Additional examination of temporal arteries (ultrasonography, biopsy) should be promptly undertaken, if there is any suspicion of coincidence with giant cell arteritis involving temporal arteries. PET/CT cannot provide evidence of temporal arteritis because the diameter of these arteries is too small. For blood vessels, the resolution capacity ranges from diameters above 4 mm [8].

On the other hand, for the type of giant cell arteritis affecting large vessels (the aorta and its main branches), PET/CT is considered a moderately sensitive and highly specific examination. Regardless of this, there is a published case of a false-negative PET/CT finding of a biopsy-confirmed giant cell aortitis in an oncologic patient [9].

The importance of fluorine-18-fluorodeoxyglucose PET/CT examination for the diagnosis of polymyalgia rheumatica still has to be determined. Although the findings may support a PMR diagnosis, they cannot be considered a confirmation of a PMR diagnosis.

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Involvement of the Aorta in GCA

11

Viera Štvrtinová, Svetoslav Štvrtina, and Jozef Rovenský

11.1 Introduction

Involvement of the aorta and its branches is found in about 10–15% GCA patients. This involvement can be life-threatening due to development of dissecting aneurysm or rupture of the aorta [1]. GCA is one of the most common vasculitides in population over the age of 50 years. Evans et al. [2] found that patients with GCA were 17.3 times more likely to develop a thoracic aortic aneurysm and 2.4 more likely to develop an abdominal aortic aneurysm compared with the general population. In a population-based study of a cohort of patients with GCA, aortic aneurysm and/or dissection developed in 18% (30 incident cases from 168 patients in the cohort) [3]. In some patients a concomitant giant cell aortitis, aortic aneurysm and aortic arch syndrome could be present [4]. Its manifold and varying clinical picture and course of the disease are probably caused by the heterogeneity of both immune and inflammatory reactions in individual patients [5].

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Aortic involvement may appear years after the initial diagnosis of GCA. Therefore, aortic involvement has probably been underestimated, and its incidence may be more frequent than suspected. Involvement of the aorta and its primary and secondary branches has been increasingly recognized [6]. Systematic evaluation of patients with imaging techniques such as magnetic resonance imaging angiography (MRA) and positron emission tomography (PET) may reveal that the clinical impact of extracranial involvement by GCA may be more relevant than previously thought [7]. Patients with biopsy-proven GCA and with coronary artery disease have increased risk of aortic aneurysmal disease and arterial thrombosis [8]. PET-CT has the ability to view the activity of the disease especially on the large thoracic vessels, including the thoracic aorta [9].

The aim of our work is to discuss typical histopathologic changes in the aorta of GCA patients.

11.2 Case Reports

11.2.1 Case 1

An 86-year-old patient with a history of coronary artery disease and peptic ulcer, after antero-septal myocardial infarction 2 years before, was admitted to the hospital for chest pain lasting for 2 h. At the time of admission, his blood pressure was 90/60 mm Hg, and the ECG showed a picture of acute myocardial infarction of the anterior wall. Urgent thrombolysis could not be carried out in the patient because of melaena, probably due to bleeding from a duodenal ulcer. Eighteen hours after admission to the hospital, the patient suddenly died.

The autopsy revealed a fresh extensive myocardial infarction of the anterior and posterior wall of the left ventricle and of papillary muscles of the mitral valve. When examining the abdominal aorta, two circular (ringlike) widenings of lumen (aneurysms) were observed below the renal artery branches, and both the iliac arteries were extended in a balloon-like way having 1.2 cm in the diameter (Fig. 11.1). One of the typical histopathologic findings in GCA is a granuloma or granulomatous inflammation of the media, as we can see in Fig. 11.2 in the abdominal aorta in our 86-year-old man. The inflammatory infiltrate contained mostly histiocytes and plasmatic cells, but few lymphocytes and one giant multinucleated cell can be seen in Fig. 11.2. In the area of granuloma, the structure of elastic fibres disappears. A typical multinucleated giant cell is shown in Fig. 11.3. All the layers of the vessel wall are involved, but the media is affected the most. Dissected and fragmented inner elastic lamina is visible in Fig. 11.4, showing also a calcium deposition in the area of the internal elastic lamina. In another histological picture of the aorta of the same patient (Fig. 11.5), we can see typical multinucleated giant cells.

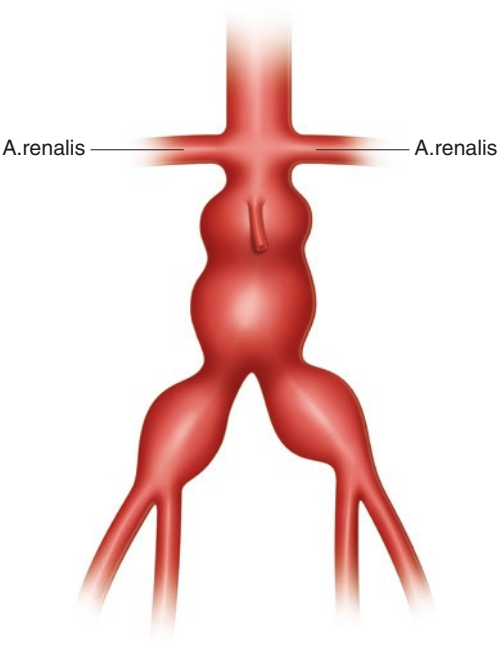

Fig. 11.1 Scheme of the aneurysms of the abdominal aorta and common iliac arteries in an 86-year-old man

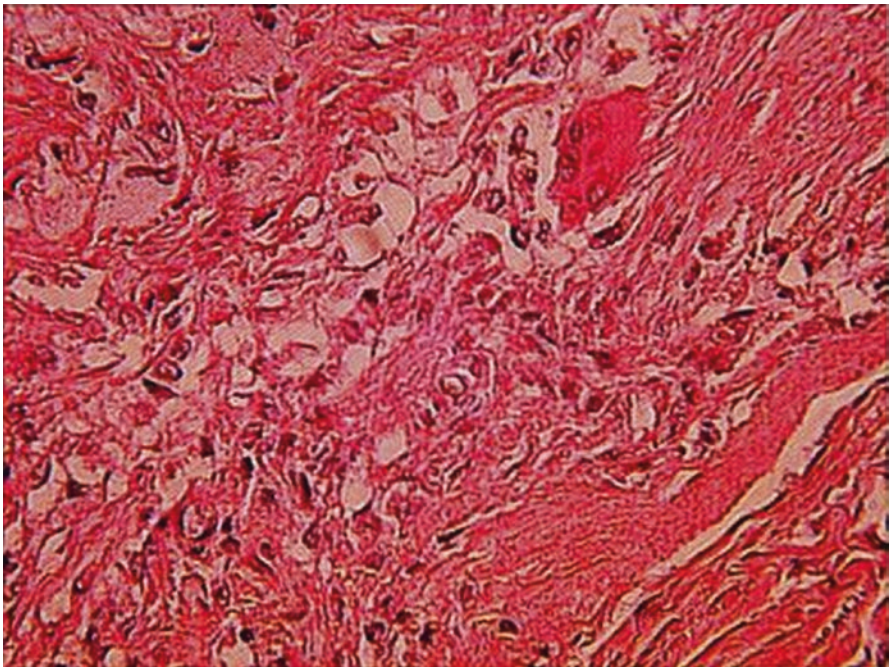

Fig. 11.2 Granulomatous inflammation of the media of the abdominal aorta. Stained with HE—haematoxylin-eosin. Inflammatory infiltration formed mainly by histiocytes and plasmatic cells, less from lymphocytes and multinucleated giant cells

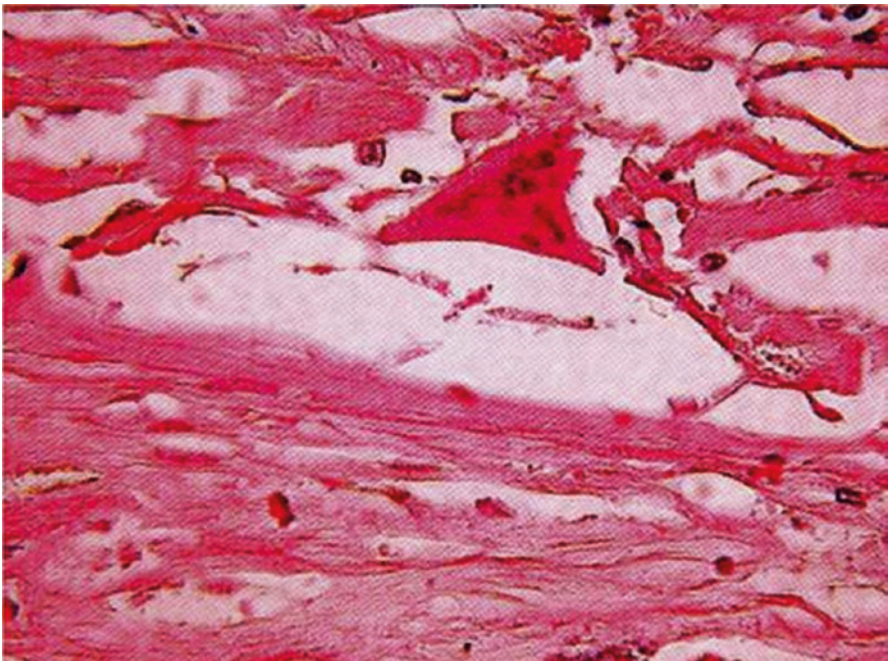

Fig. 11.3 Multinucleated giant cell. Stained with HE

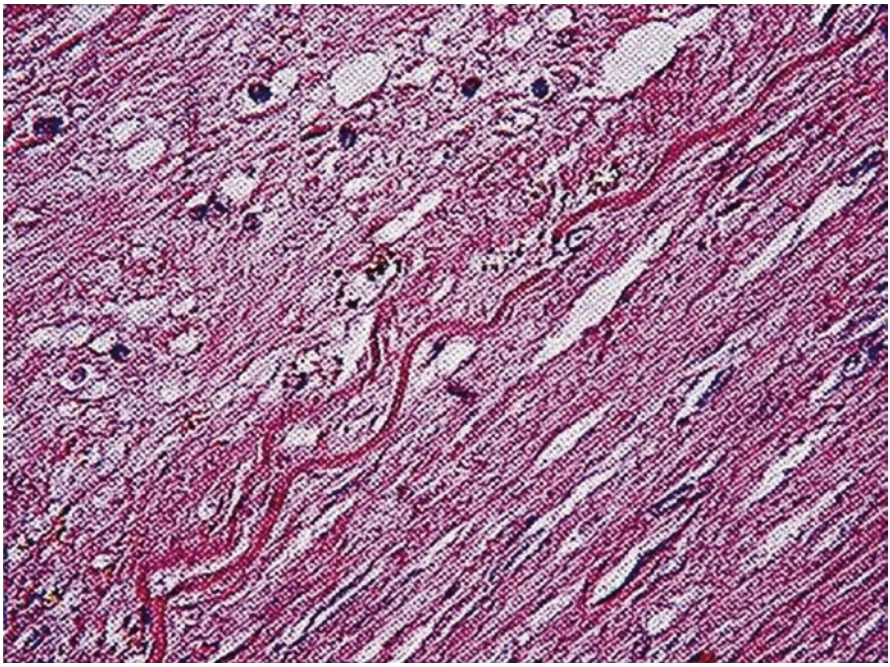

Fig. 11.4 Dissected and fragmented internal elastic lamina. Stained with HE

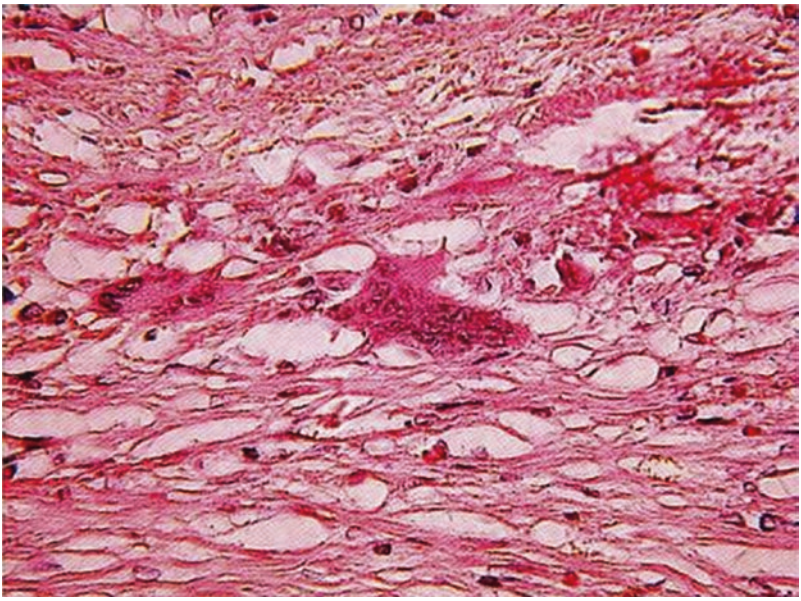

Fig. 11.5 Multinucleated giant cells. Stained with HE

11.2.2 Case 2

An 84-year-old woman with the history of arterial hypertension and coronary artery disease was admitted to a hospital for quantitative disturbance of consciousness (sopor to coma) with 110/70 mm Hg blood pressure. ECG showed sinus bradycardia (with 50/min frequency) with no signs of an acute coronary syndrome. Her blood count showed severe anaemia (haemoglobin—5.4 g/L) and leucocytosis (11×10^9/L). Cerebral CT did not show any fresh ischaemic or haemorrhagic lesion. The patient died after 6 h of hospitalization.

Macroscopic examination during her autopsy discovered a 3.5 cm long longitudinal tear at the posterior wall of the aorta, which starts 2 cm above the aortal valve. The tear made a haematoma cavity between adventitia and media. The cavity continued to the abdominal aorta, and there, at the level of truncus coeliacs, a crosswise 1 cm long fissure was found at the posterior wall of the aorta through which the blood poured back to the lumen of the aorta. A dissecting aneurysm of the ascending thoracic aorta, which continued to the descending thoracic and abdominal aorta (Fig. 11.6), was the cause of death of the patient. Histological investigation of the aortic wall revealed that aneurysm developed due to giant cell arteritis (GCA). Panarteritis with mixed inflammatory infiltrate (Fig. 11.7) was found in some parts of the aorta, whereas the other parts show atrophy of smooth muscles of the media together with pronounced calcifications. Typical deposits of calcium salts in the aorta of our patient (Fig. 11.8) can be seen in the area of the internal elastic lamina; in the intima, we can see atherosclerotic plaque with calcium. Figure 11.9 shows calcium deposition in the area of the internal elastic lamina in the same patient.

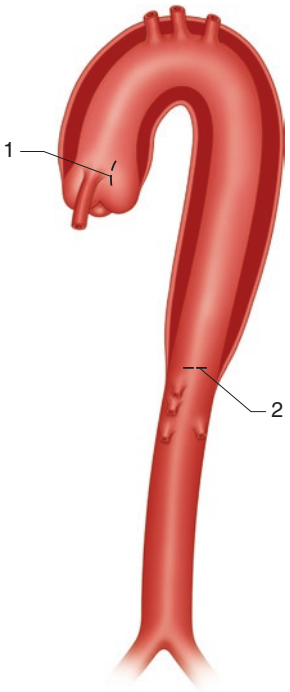

Fig. 11.6 Scheme of dissecting aneurysm of the thoracic and abdominal aorta in an 84-year-old woman: (*1*) beginning of the dissection, (*2*) end of the dissection

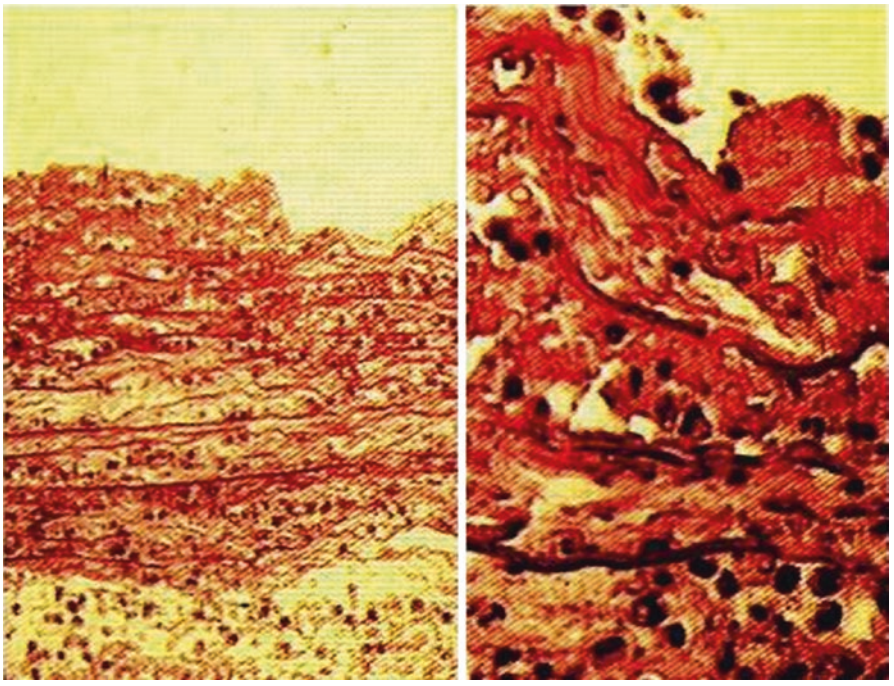

Fig. 11.7 Panarteritis—mixed inflammatory infiltrate. Stained with haematoxylin-eosin (HE)

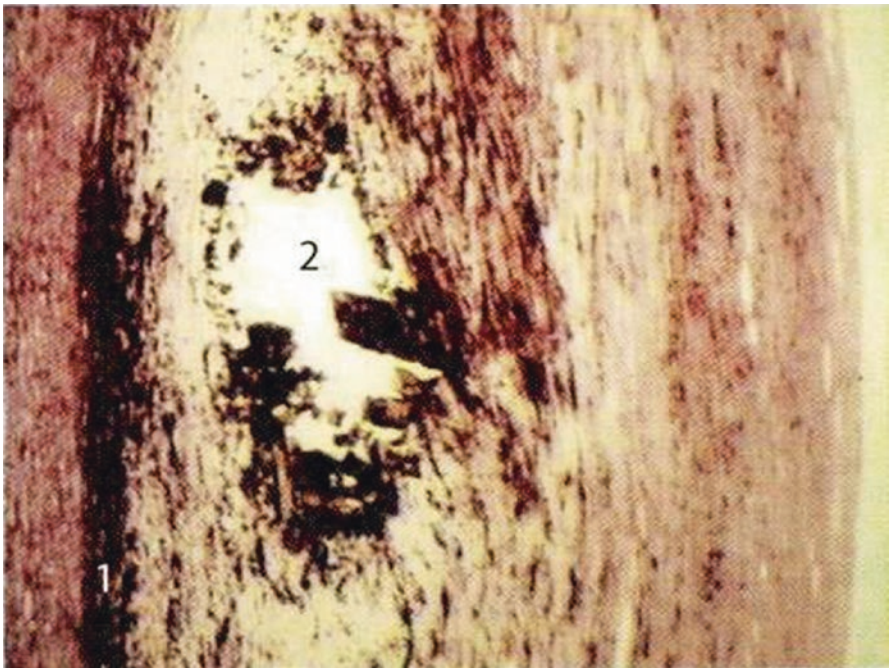

Fig. 11.8 Calcium deposits (*1*) in the internal elastic lamina, sclerotic plaque with calcium in intima (*2*). Stained with Kossa and HE

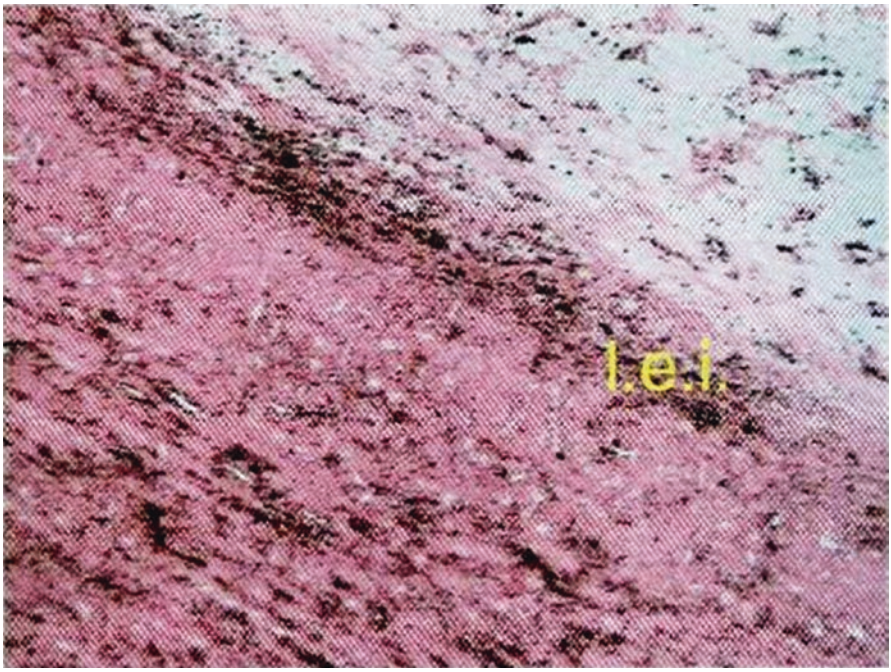

Fig. 11.9 Typical calcium powder in the internal elastic lamina. Stained with Kossa and HE

11.2.3 Case 3

An 81-year-old patient with the history of two myocardial infarctions with an implanted pacemaker was admitted to hospital for strong, intensive pressure pain across a large area in the front part of the chest. ECG showed a pacemaker rhythm with frequency of 70/min and the condition after antero-septal and lateral myocardial infarction. His values of enzymes indicating myocardium damage—CK, AST and ALT—were normal, just as his blood count. After 20 h of hospitalization, suddenly both his breathing and heart stopped, and the clinician supposed another acute heart attack.

At autopsy, a 4 cm long longitudinal tear was discovered at the superior wall of the aorta, 0.4 cm above the aortal valve. The tear made a sac between the adventitia and the media 8 cm long, filled with dark red clots (Fig. 11.10). The cause of death in this patient was giant cell arteritis with dissecting aneurysm of the ascending aorta. The fresh myocardial infarction supposed by clinician was not proven by autopsy. The histological pictures of this 86-year-old patient's aorta showed mixed inflammatory infiltrate (Fig. 11.11) and neovascularization (Fig. 11.12) in the media of the aorta with inflammatory infiltration and destruction of elastic fibres of the media.

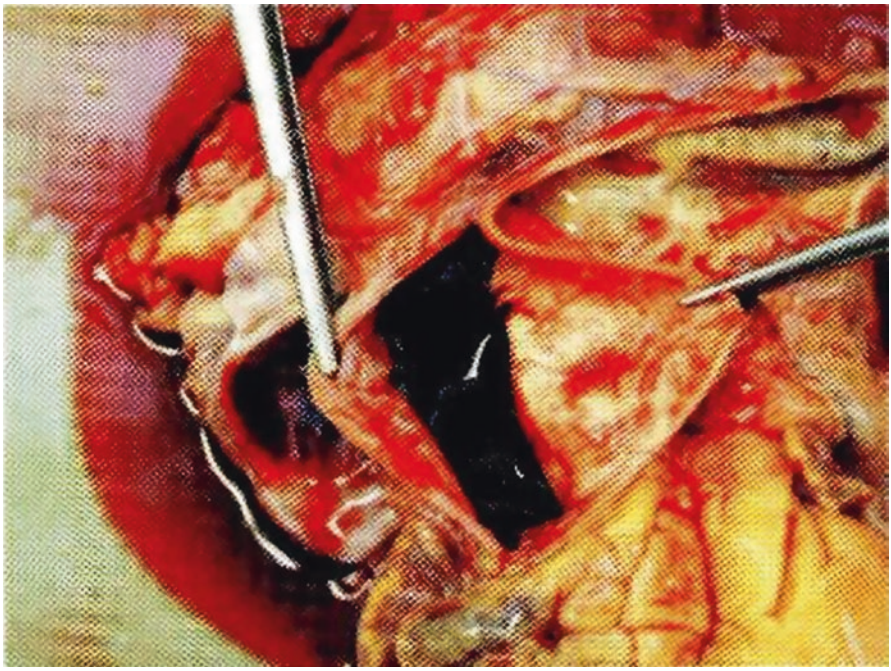

Fig. 11.10 Macroscopic photography of the aortic arch—dissection of the aortic wall with blood coagulum

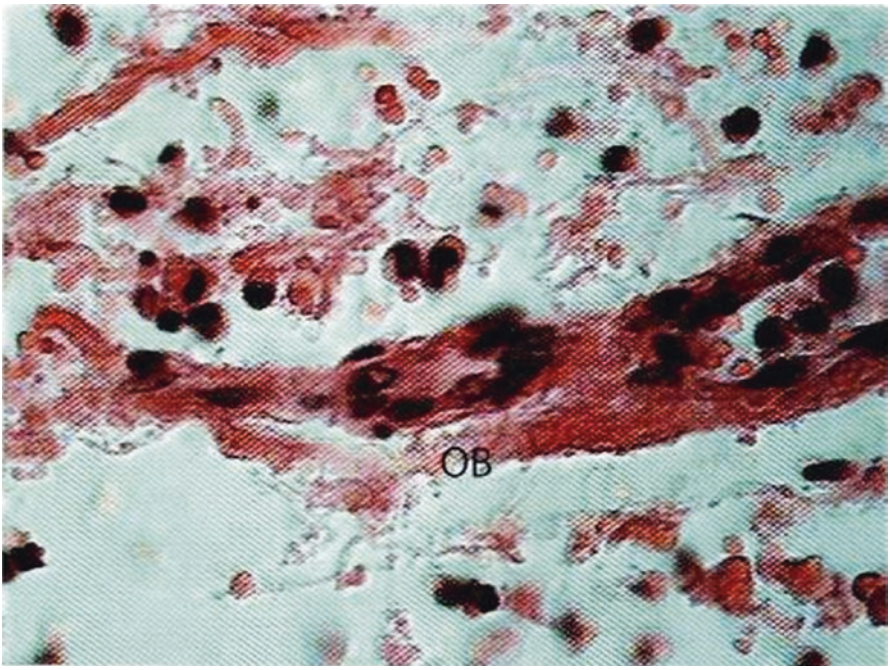

Fig. 11.11 Aortic wall—mixed inflammatory infiltrate, histiocytes and giant cell (*OB*) in adventitia. Stained with HE

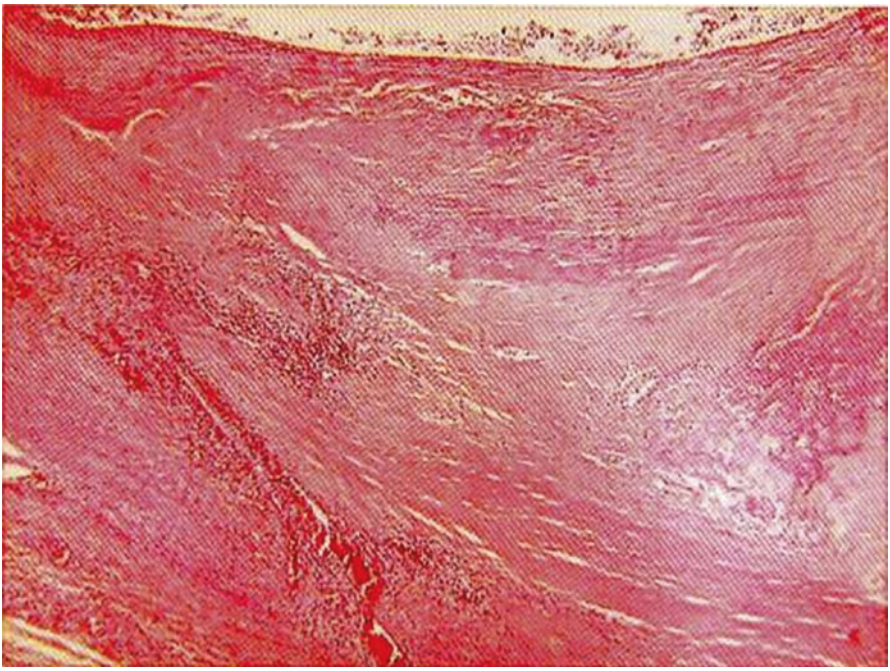

Fig. 11.12 Neovascularization in the media of the aorta

11.3 Discussion

Giant cell arteritis, which involves medium-size and large arteries, can be lethal, and it is often manifested in a dramatic way, via dissection or rupture of the aorta in the elderly, but also by myocardial infarction or stroke [10]. GCA significantly increases a risk of aorta aneurysm presenting often as a late fatal complication of the disease. Clinically occult GCA has been demonstrated in almost 50% of patients before aortic dissection [11]. N. Espinola-Zavaleta et al. describe a rare case of acute aortic dissection without preceding aneurysm secondary to histologically confirmed giant cell arteritis (GCA) in an 85-year-old female with a 4-year history of polymyalgia rheumatica and temporal arteritis diagnosed per biopsy 6 months prior to presentation [12].

In the UK, General Practice Research Database (GPRD) comparing the GCA cohort (6999 patients) with the non-GCA cohort (41,994 controls) revealed that the adjusted subhazard ratio (95% CI) for aortic aneurysm was 1.92 (1.52–2.41). Significant predictors of aortic aneurysm were being an ex-smoker (2.64 (2.03–3.43)) or a current smoker (3.37 (2.61–4.37)), previously taking antihypertensive drugs (1.57 (1.23–2.01)) and a history of diabetes (0.32 (0.19–0.56)) or cardiovascular disease (1.98 (1.50–2.63)). This study confirmed that patients with GCA have a twofold increased risk of aortic aneurysm, and this should be considered within the range of other risk factors including male gender, age and smoking. The protective effect of diabetes in the development of aortic aneurysms in patients with GCA was also demonstrated [13].

The character of inflammatory damage in GCA is segmental. The intensity of inflammatory response differs in different parts of the same vessel and in individual vessels, and it varies in different stages of the disease as well [14]. The classical picture of granulomatous inflammation with giant cells is observed in 50% of patients; the other half of patients with positive histological finding show panarteritis with mixed inflammatory infiltrate that has mainly lymphomononuclear character with some neutrophils and eosinophils but with no giant cells [15]. Such panarteritis, developed into mixed inflammation consisting of polymorphonuclear leucocytes, lymphocytes and plasmocytes, is obvious from Fig. 11.7. Two stages of inflammation are discerned in GCA [16]. In atrophic arterial segments, a focal, foreign body, giant cell reaction to the calcified internal elastic membrane is found, but in other biopsies, a different picture with a diffuse macrophage attack on the media and the intima with numerous and apparently macrophage-derived giant cells, which did not attack calcification, is seen. Morphologically, the inflammatory process appears to be initiated by a foreign body giant cell attack on calcified internal elastic membrane in arteries and on calcified atrophic parts of the aortic media. The ensuing diffuse chronic inflammation leads to vessel wall dilatation and extensive intimal thickening. The latter, which relates to the production of promoting factors by the inflammatory cells, causes arterial stenosis and ischaemic complications [17].

Giant cells obviously "attack" the inner elastic membrane and incorporate the calcified parts of the membrane. It seems that calcification in the area of the internal elastic lamina and the atrophy of media are inevitable prerequisites for development of inflammatory response [18]. Calcification of the inner elastic membrane differs morphologically from the calcification developed in Monckeberg medial sclerosis and from atherosclerotic calcifications [19]. This is shown also in Fig. 11.8, and this morphological difference will probably be a reason that giant cells start to gather around calcium in the internal elastic lamina. The analysis of vessel segments that are not affected by the inflammatory response showed a significantly greater atrophy of smooth muscles of the media and also calcifications in the area of the inner elastic lamina compared with the group of healthy volunteers. Involvement of arteries at the beginning of disease can be caused by metabolic disorders in the arterial wall. That gradually leads to the atrophy of smooth muscles of media and to degeneration and dystrophic calcifications of the inner elastic membrane. Giant cells developing around foreign corpuscles come probably from smooth muscles, and then they respond to the presence of degenerated and calcified inner elastic lamina [17]. Because of the high age of patients with GCA, vasculitis can set in the vascular wall already damaged by the atherosclerotic process, and the inflammatory response can be triggered by a so far unknown mechanism [20]. Thus, in patients with GCA, we can see atherosclerotic as well as vasculitic changes as it is evident from Figs. 11.8 and 11.9, where incorporation of calcium into the internal elastic lamina is a typical sign of vasculitis and atherosclerotic plaque in the intima layer is a characteristic sign of atherosclerosis.

T cells emerge as the key players in inflammation-associated injury pathways. In GCA, all injury mechanisms have been related to effector macrophages. Macrophages in the adventitia focus on production of pro-inflammatory cytokines. Macrophages in the media specialize in oxidative damage with lipid peroxidation attacking smooth muscle cells and matrix component. These macrophages also supply reactive oxygen intermediates that, in combination with nitrogen intermediates, cause protein nitration of endothelial cells. Production of oxygen radicals is complemented by production of metalloproteinases, likely essential in the breakdown of elastic membranes. With fragmentation of the internal elastic lamina, the intimal layer becomes accessible to migratory myofibroblasts that later cause hyperplasia of the intima and occlusion of the vessel lumen [21]. Development of a hyperplastic intima is accompanied by intensive neoangiogenesis. While in normal arteries the presence of vasa vasorum is restricted to the adventitia, in the case of inflamed arteria, the capillaries grow into the media and the intima [22]. Neovascularization is present also in the aorta of our 86-year-old patient (Fig. 11.12).

Diagnosis of GCA is made through characteristic histological finding, revealed at biopsy of the temporal artery or from the material taken during surgery [23]. Because involvement of the vessels is segmental, meaning that biopsy may not happen to hit the right spot, histological examination of several cuts is recommended: the sections shall be taken from 5–8 cm big area of the temporal artery [24], the

minimum being 2–3 cm big spot. Biopsy should be carried out before the therapy is started, since corticoid treatment decreases the value of histological examination [15]. If biopsy is done before the therapy starts, it is beneficial in 80% of cases; if it is made in the first week of treatment, it is still positive in 60% of cases; however, a biopsy carried out a week after full treatment by corticoids is positive only in 20% of patients [25].

The survival of patients is not significantly shortened by the presence of giant cell arteritis [26], under the condition that the disease is early enough and properly treated. Säve-Soderbergh et al. [14] describe following causes of death in nine GCA patients—two patients died of myocardial infarction, two of dissecting aneurysm and five of stroke. None of the patients described was administered adequate corticoid therapy. Lie [10] reports 18 patients with extracranial GCA, with these causes of death: rupture of aortal aneurysm in six patients, dissection of the aorta in six patients, cerebral infarction in three patients and myocardial infarction in three patients.

As involvement of large arteries in GCA may have fatal consequences, in all patients, it is recommended to look for changes in these arteries in a focused way. Blood pressure shall be measured in both upper extremities. Methods that enable to assess the extent of arterial system affliction include ultrasound, MRI and angiographic examination. GCA significantly increases the risk of development of aortal aneurysm that often presents a late complication of a disease that may cause death of patients. That is why it is necessary to actively seek aneurysms in all GCA patients and make regular duplex ultrasonography examinations, where appropriate, supplemented with CT or MR examinations. Patients with diagnosed GCA shall be carefully and properly treated, since in most of the patients in which aortal dissection developed, the treatment was not adequate.

It is also important to treat hypertension as high blood pressure was found in 77% of patients with dissecting aorta. Untreated or insufficiently treated hypertension is one of the important factors contributing to occurrence of dissecting aortic aneurysm. It is also necessary to adhere very strictly to the treatment regime. The majority of cases with a preceding history of GCA were on low doses of steroids or on no treatment at the time of dissection, and the median erythrocyte sedimentation rate of these patients was 62 mm per hour [27].

Conclusion

Giant cell arteritis involving the aorta can be a lethal disease, and it is often manifested in a dramatic way in the elderly: by dissection or rupture of the aorta. Early diagnosis, correct treatment and lifelong checks of patients in whom GCA was diagnosed can prevent them from development of such a severe complication as aortic aneurysm.

Typical histopathologic changes in GCA include granulomatous inflammation, presence of giant cells—especially in the media—atrophy of smooth muscles and destruction of elastic fibres, splitting and fragmentation of the internal elastic lamina, as well as deposition of calcium salts into the area of the internal elastic lamina, diffuse inflammation of vessel wall and ingrowth of capillaries (neovascularization).

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Biologicals: A Perspective for the Treatment of PMR/GCA

12

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Polymyalgia rheumatica and giant cell arteritis are diseases with an exceptionally favorable response to glucocorticoid (GCs) treatment. It is well known and a consensus that corticosteroid therapy usually leads to a rapid and dramatic improvement of patients' complaints and returns them to previous functional status [1, 2]. Almost immediate pain relief after initiation of corticosteroids can be regarded as an additional diagnostic feature for PMR [3]. If no significant pain reduction can be achieved by an adequate steroid dose, the diagnosis must be seriously, and maybe repetitively, reconsidered.

However, neither GCs nor alternative treatments had been studied in a controlled way with respect to initial dosing and duration of therapy until the GIACTA (NCT01791153)—a Phase III, global, randomized, double-blind, placebo-controlled trial investigating the efficacy and safety of Tocilizumab as a novel treatment for GCA had been carried out. The recommended GCs initial dosages vary to a high degree and are based rather on experience than on evidence [4, 5]. While glucocorticoids (GCs) are the cornerstone of therapy and can reduce the risk of visual loss, they may also be toxic, especially for older patients. Relapses are common in PMT/GCA, and given the side effects of GCs, adjunctive treatment options are highly necessary [6–8].

Nevertheless, it is mandatory to consider all risks for and contraindications of GC treatment. The long-term daily glucocorticoid doses applied for PMR treatment do not usually exceed 15 mg [5]. Lower initial doses have been also reported in several publications. However, some authors consider 10 mg/day as an insufficient dose, because maintaining the disease in remission was only possible administering

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15–20 mg/day [4, 5]. The current experience considers an initial dose from 25 to 15 mg prednisone/day as the most appropriate one [1, 4, 5]. The therapeutic effect should be evaluated after 1 month of treatment as the goal of initial treatment is to achieve remission during the first 4 weeks of the disorder [9]. In daily practice, we reduce the corticosteroid dose by 2.5 mg of prednisone every 4 weeks. Maintenance daily prednisone doses should not exceed 5–7.5 mg and should be applied for at least a 12-month period [1]. Some patients must be kept on treatment for 2 years and a little percentage even for 4–5 years.

The severity of PMR shows high variations. In GC refractory cases and to avoid respective side effects, immunosuppressive drugs including cyclophosphamide, azathioprine, methotrexate, and—historically—dapsone have been studied as steroid-sparing agents with sometimes inconclusive results [10–13]. Toxicity can be a significant problem, particularly with dapsone and cyclophosphamide.

Azathioprine, in an average dosage of 1.5–2.5 mg/kg/day, reduced steroid requirements in a double-blind, placebo-controlled study that included 31 patients with GCA, polymyalgia rheumatica, or both. The advantage of azathioprine over placebo, though, did not appear statistically significant until 1 year [10].

In clinical routine MTX is frequently used as a steroid-sparing agent, in doses of 15–25 mg/week. However, with respect to its efficacy, doubts remain. In a formal meta-analysis, additional MTX, 7.5–15 mg/week, reduced the risk of a first relapse by 35% and of a second relapse by 51%. In addition, the cumulative dose of GCs could be reduced. The superiority of the treatment effect of methotrexate over placebo, though, fully appeared only earlier than after period of 24–36 weeks; moreover, no between-group difference was noted in the occurrence of adverse events [11].

Some, but restricted evidence suggests that cyclophosphamide may be the immunosuppressant most consistently effective. It may allow quicker steroid reduction when initiated after a relapse and may be administered in monthly pulses [12].

12.1 Anti-T-Cell Therapy

As the role of biologics in the treatment of rheumatic diseases expanded continuously, researchers and clinicians commenced to study TNF-alpha inhibitors in PMR/GCA. Research had revealed increased expression of TNF-alpha in the temporal artery specimens of patients with GCA [14].

Tumor necrosis factor (TNF) inhibitors (e.g., infliximab, etanercept) have been evaluated in clinical trials for the treatment of GCA and PMR. A randomized controlled trial showed that adding infliximab (IFX) to steroids provided no measurable benefit in the management of newly diagnosed GCA [15].

A double-blind, placebo-controlled trial of etanercept (ETA) in steroid-refractory GCA yielded mixed results. The study included 17 patients who required a stable dose of prednisone of 10 mg/day to maintain clinical remission and had at least one steroid-related adverse effect. After 12 months, more of the patients in the etanercept group had successfully discontinued prednisone (50%

versus 22.2% of placebo patients), but the difference was not significant. No difference was noted in the number and type of adverse events. However, patients in the etanercept group did have a significantly lower cumulative dose of accumulated prednisone during the first year of treatment ($p = 0.03$). The researchers noted that a larger trial with longer follow-up is needed to determine the role of etanercept in GCA therapy [16].

A randomized, placebo-controlled trial including 51 patients with newly diagnosed polymyalgia rheumatica and associated giant cell arteritis and without prior GCs treatment was carried out in Italy to compare the efficacy of prednisone plus infliximab with that of prednisone plus placebo in patients with newly diagnosed polymyalgia rheumatica. Patients received initial therapy with oral prednisone tapered from 15 to 0 mg/day over 16 weeks per a standard protocol, plus infusions of placebo or infliximab, 3 mg/kg of body weight, at weeks 0, 2, 6, 14, and 22. The proportion of patients who were free of relapse and recurrence at 52 weeks did not differ between groups as well as all secondary outcomes at weeks 22 and 52 did not differ between the groups. Although too small to be definitive, the trial provided evidence that adding infliximab to prednisone for treating newly diagnosed polymyalgia rheumatica is of no benefit and may be harmful [17].

To elucidate a potential role of etanercept (ETA) in the treatment of PMR, a randomized controlled trial including 20 newly diagnosed, glucocorticoid (GC)-naïve patients with PMR and 20 matched non-PMR control subjects was carried out. The primary outcome was the change in PMR activity score (PMR-AS) [18]. Secondary outcomes were changes in erythrocyte sedimentation rate, as well plasma levels of TNF-alpha and interleukin (IL) 6, and patients' functional status (health assessment questionnaire) and cumulative tramadol intake during the trial. In ETA-treated patients, the PMR-AS decreased by 24% ($p = 0.011$), reflecting significant improvements in shoulder mobility, physician's global assessment and C-reactive protein, and insignificant ($p > 0.05$) improvements in duration of morning stiffness and patient's assessment of pain. In parallel, ESR and IL-6 were reduced ($p < 0.05$). Placebo treatment did not change PMR-AS, ESR, and IL-6 ($p > 0.05$). Functional status did not change and tramadol intake did not differ between patient groups. Etanercept monotherapy reduced disease activity in GC-naïve patients with PMR; the effect, though, appeared to be modest, which the authors interpreted as indicating a minor role of TNF-alpha in PMR [19].

Applying TNF inhibitors in PMR/GCA could not question the role of GCs as cornerstone of treatment for these diseases. Although two studies revealed no benefit from adding infliximab to prednisone in patients with GCA or PMR, some corticosteroid-sparing effect for TNF-blockers in these two conditions cannot be completely excluded, as the trials were too small to definitively identify small benefits. It could be possible that TNF-blocking agents are effective in subsets of patients with polymyalgia rheumatica and GCA characterized by a more chronic, relapsing course [20]. As virtually all clinical trials using TNF-alpha inhibitors in PMR/GCA have failed, it can be regarded current consensus that in these patients their use cannot be generally recommended.

Other biologic therapeutics are also of interest in these related diseases. Another treatment directed against T-cells was the subject of a multicenter clinical trial evaluating the efficacy of abatacept in GCA, which was recently completed. This study provides the first trial-level evidence in patients with GCA, that the addition of abatacept to a standard treatment regimen with prednisone reduces the risk of relapse of vasculitis and is not associated with a higher rate of toxicity compared to prednisone alone. The median duration of remission (9.9 vs. 3.9 months) was significantly higher among patients receiving abatacept compared with placebo. However, this remains a pilot study, and replication in larger cohorts is necessary [21].

12.2 Anti-IL-6 Treatment

GIACTA (NCT01791153) is a Phase III, global, randomized, double-blind, placebo-controlled trial investigating the efficacy and safety of Tocilizumab as a novel treatment for GCA. It is the largest clinical trial ever conducted in GCA and the first to use blinded, variable-dose, variable-duration steroid regimens based on a handful of studies with in part convincing beneficial results of the application of anti-IL-6 therapy in PMR/GCA patients [22].

In an open-label controlled trial, 12 patients treated with TCZ achieved a PMR-AS in the low disease activity range at week 12, accompanied by a significant reduction of GC intake and at a reasonable tolerability [23].

In another controlled trial with TCZ between 2012 and 2014, 20 GCA patients were randomly assigned to receive tocilizumab and prednisolone and 10 patients to receive placebo and GC; 17 (85%) of 20 patients were given tocilizumab, and 4 (40%) of 10 patients given placebo reached complete remission by week 12, which is statistically significantly different. Relapse-free survival was achieved in 17 (85%) patients in the tocilizumab group and 2 (20%) in the placebo group by week 52. Seven (35%) patients in the tocilizumab group and five (50%) in the placebo group had serious adverse events [24].

The multicenter GIACTA (NCT01791153) study was conducted in 251 patients across 76 sites in 14 countries. The study's primary endpoint was the proportion of patients achieving sustained disease remission at week 52. The secondary endpoints were the time to first GCA flare after clinical remission, cumulative corticosteroid dose at week 52, and safety outcome measures.

While not available for peer review, sponsor-released preliminary results suggest efficacy, and the Phase III study, the largest clinical trial ever conducted in GCA, is said to meet its primary and key secondary endpoints. The primary endpoint of the study was met, with TCZ—initially combined with a six-month steroid taper regimen—significantly increasing the proportion of patients achieving sustained remission at 1 year (56% [QW; $p < 0.0001$] and 53.1% [Q2W; $p < 0.0001$]) versus 14% with a six-month steroid taper regimen given alone [22]. The study also met its key secondary endpoint, demonstrating that TCZ—initially combined with a six-month steroid taper regimen—significantly increased the proportion of patients achieving

sustained remission at 1 year (56% [QW; $p < 0.0001$] and 53.1% [Q2W; $p = 0.0002$]) compared to 17.6% with a 12-month steroid taper regimen given alone. No new safety signals were observed, and these results are consistent with TCZ's documented safety profile in rheumatoid arthritis [22]. The GIACTA data will be submitted for presentation at an upcoming medical conference and to regulatory authorities around the world for approval and consideration.

12.3 Concluding Remarks

During the last years, tocilizumab, the only interleukin-6 inhibitor currently available—a bundle of IL-6 inhibitors being in the pipeline—has shown increasing promise in treating PMR and GCA but also Takayasu's arteritis, the third large vessel vasculitis, preferentially afflicting young women. Several clinical trials of PMR/GCA are either actively recruiting or are active but not yet recruiting. It may, moreover, be anticipated that other IL-6 inhibitors also will exert a beneficial effect on large vessel vasculitides as well as on PMR, as those diseases are commonly considered to constitute IL-6-driven diseases [25]. This would be a significant step forward in managing these diseases, with abatacept showing some perspective results on the horizon [26].

The rheumatological community's initial disappointment caused by the unforeseen relative inefficacy of TNF inhibitors in GC refractory cases of large vessel vasculitides could be followed by enthusiasm about new opportunities for patients with large vessel vasculitides. Frequently, these patients are at higher ages, carrying contraindications and risk factors for GCs; therefore, an alternative will be highly appreciated. Of course, not only but also for financial reasons, GC will remain the anchor drug for treating PMR and GCA; however, the perspectives for patients not adequately responding to steroids can be regarded around the house corners as improved.

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Monitoring Tools for Polymyalgia Rheumatica/Giant Cell Arteritis

13

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Usually, polymyalgia rheumatica shows a rapid onset with severe and symmetric muscle pain in the shoulder girdle and the neck, less often in the pelvic girdle, accompanied by muscle tenderness. Patients suffer from continuous pain, often aggravated during physical inactivity or the night. Sometimes transient synovitis occurs without radiological signs of arthritis (see Table 13.1) [1]. Approximately, two thirds of patients with giant cell arteritis have new-onset headache. This headache is often present daily and is quite bothersome. The headache may be generalized, but it is more commonly unilateral and localized to the temporal area. When headache is absent or mild, the index of suspicion for the disorder is frequently low, and the diagnosis may be delayed for weeks or even months [2].

Polymyalgia rheumatica and GCA are frequently accompanied by several nonspecific symptoms, such as lethargy, depression, fatigue, as well as fever, loss of appetite and weight, and overall weakness. They may also have various visual symptoms, including blurring and scotomas. The onset of these symptoms may be abrupt or insidious. Jaw claudication in patients more than 50 years of age has high specificity but only moderate sensitivity (45–50%) for giant cell arteritis. Pain on chewing may be unilateral, but it is more often bilateral and frequently involves the masseter and temporalis muscles [3].

To make things complicated, there is no specific positive finding that confirms both diseases; therefore, a variety of criteria sets for the classification of patients as suffering from PMR/GCA have been developed targeting reasonable sensitivity and specificity [4, 5]. These criteria will be discussed in detail elsewhere in this book.

In 1997 a European collaborative PMR-working group was commissioned by ESCISIT (EULAR Standing Committee on Clinical Trials including Therapeutic

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Table 13.1 Bird/Wood criteria for PMR [1]

1. Bilateral shoulder pain and/or stiffness
2. Duration of onset of 2 weeks or less
3. Initial ESR >40 mm/h
4. Duration of early morning stiffness >1 h
5. Age 65 years or more
6. Depression and/or weight loss
7. Bilateral upper arm tenderness
Probable PMR: any three or more of these criteria *or* <3 criteria with a clinical abnormality of temporal artery
Further proposed: Definite PMR would be probable MRR with a positive response to steroid therapy using a single blind therapeutic test of steroid against placebo

Trials). One of the two objectives of this task force was a sensitivity analysis of the existing classification criteria sets, by means of a pan-European observation. The other one was the first-time development of PMR response criteria to provide a possibility to monitor the disease process and the therapeutic response [6]. The European collaborative PMR group comprised eight centers covering all parts of the continent (Leeds, UK; Stockerau, AUT; Ljubljana, SLO; Kaunas, LIT; Pavia, ITA; Jerusalem, ISR; Tartu, EST; Piestany, SLK).

All patients were interviewed with respect to full medical history and were examined physically, with all the features of existing diagnostic criteria having been evaluated [2–6]. The diagnosis of PMR was finally established by experienced clinicians. The Bird/Wood [2] criteria performed best with a sensitivity of 99.5%, and the Chuang/Hunder [3] criteria achieved the second place, with a sensitivity of 93.3%, in identifying patients from the group of 213 patients considered suffering from PMR by ten experienced investigators from all across Europe [7]. Of the four criteria sets compared, these both performed significantly better than the two other criteria sets, though each of these was admittedly developed for rather specialized reasons. The identification range was found to be between 99.5% (Bird/Wood) and 67.8% (Nobunaga) for the sets of criteria applied [7]. Thus, both criteria sets providing more than 90% sensitivity during this observation, namely, the Bird/Wood criteria and the Chuang/Hunder criteria, could be recommended for classifying PMR patients in daily routine as well as in clinical trials.

In 1990, the American College of Rheumatology (ACR) published the following criteria for classifying GCA [8] (see Table 13.2). The patient can be classified as suffering from GCA, if three of the five classification criteria are fulfilled, achieving a sensitivity of 93.5% and specificity of 91.2%.

The Bird/Wood criteria were shown to have a high sensitivity to detect patients with PMR; their specificity, though, was not investigated during the aforementioned studies. So, no unambiguously accepted criteria were available until the ACR and EULAR commissioned a task force to develop new classification criteria for PMR. In a stepwise procedure including the Delphi technique, the provisional ACR/

Table 13.2 1990, American College of Rheumatology (ACR) criteria for classifying GCA [5]

1. Age above 50
2. Newly occurred headache
3. Tenderness or decreased temporal artery pulsation
4. Increased erythrocyte sedimentation rate exceeding 50 mm/h
5. Biopsy-proven necrotizing arteritis with mononuclear infiltrate or granulomatous

A patient can be classified as suffering from GCA if three of the five classification criteria are fulfilled

Table 13.3 PMR classification criteria (2012): required criteria: age >50 years, bilateral shoulder aching, and abnormal CRP and/or ESR [9]

	Points without US (0–6)	Points with US (0–8)
Morning stiffness duration >45 min	2	2
• Hip pain or limited range of motion	1	1
• Absence of RF or ACPA	2	2
• Absence of other joint involvement	1	1
• At least 1 shoulder with subdeltoid	NA	1
• Bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least 1 hip with synovitis and/or trochanteric bursitis		
• Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	NA	1

4 or more is categorized as polymyalgia rheumatica (PMR) without ultrasound (US); a score of 5 or more is categorized as PMR in the algorithm with US

EULAR classification criteria for PMR were developed and published in April 2012 [9] (see Table 13.3). In any case the reader should always be aware that classifying a patient as suffering from a disorder does not mean the same as making a diagnosis. These most recent criteria, which will be applied in further clinical trials, were the very first including also sonographic findings [9]. However, some authors did not find a significant contribution of ultrasound to the sensitivity and specificity of these new criteria [8]. According to the recent evidence at the critical value of four (maximum of six) or five including Ultrasound features (maximum of eight), their sensitivity was shown to be approximately 90% and their specificity 58% to 90% (including ultrasound) when tested against all non-PMR cases [10, 11].

13.1 Monitoring of PMR and GCA

Polymyalgia rheumatica and giant cell arteritis are diseases with an exceptionally favorable response to glucocorticoid treatment. It is well known and consensus that corticosteroid therapy usually leads to a rapid and dramatic improvement of patients'

complaints and returns them to previous functional status [7, 12]. Almost immediate pain relief after initiation of corticosteroids can be regarded an additional diagnostic feature for PMR [1]. If no significant pain reduction can be achieved by an adequate steroid dose, the diagnosis must be seriously reconsidered.

However, neither corticosteroids nor alternative treatments have been studied in a controlled way up to now, with respect to initial dosing and duration of therapy [13]. The dosages used initially vary to a high degree and are based rather on experience than on evidence [14, 15]. The EULAR response criteria for PMR and the PMR-disease activity score (PMR-AS) were developed based on corticosteroid treatment [6, 16]. As expected, patients showed a quick and impressive response after the initiation of corticosteroids during these studies.

Even though corticosteroid therapy constitutes an established measure in the treatment of PMR, no validated response criteria had been available for PMR since Barber had described the disease in 1957 [6]. The gold standard of monitoring consisted of measurement of the acute phase response and patient's global assessment [17].

The first-time development of response criteria was the one of the European collaborative PMR-working group's objectives. A questionnaire consisting of clinical parameters and laboratory values was developed and approved by a consensus meeting of the participating investigators. For known difficulties in standardizing clinical evaluation, muscle tenderness was chosen as the only investigator-dependent procedure. Laboratory examinations were performed locally per the local standards and quality control regulations [4].

Seventy-six patients from all over Europe were included into this survey (69 female and 7 male patients). The observation period lasted for 48 weeks. In addition, another 24 patients recruited from the Centre for Rheumatology, Lower Austria, were assessed per the same protocol [6].

Patients were treated exclusively by corticosteroids; the starting dose was at the discretion of the local investigator. The initial dose amounted to a mean of 24.68 (±28.61 SEM) mg prednisolone equivalent, indicating a high variability of the starting doses applied in the single centers. The initial dose could be tapered down to a mean of 7.68 (±3.61 SEM) mg at week 24 ($p < 0.0001$). The corticosteroid response time was evaluated by asking the patient for the onset of improvement after the first corticosteroid dose and amounted to 35.4 h ±18.93 [6].

Thus, the expected, rapid, and sustained response to glucocorticoid therapy was observed. Along with the reduction of corticosteroids, nearly all parameters of disease activity showed highly significant improvement, indicating decrease of inflammatory activity, reduction of pain, and amelioration of functional status of the patients [5].

Subsequently, a core set of parameters, the EULAR response criteria for PMR, was elaborated comprising the ESR or CRP, representing the acute phase response, and the VAS (visual analogue scale) of patient's pain, physician's global assessment (Phage), morning stiffness (MST), and the ability to elevate the upper limbs, representing the clinical situation [6]. Regression and correlation analysis revealed that every single parameter of the core set is significantly influencing the individual response rate with the highest weight for VAS pain, followed by physician's

Table 13.4 EULAR response criteria for PMR [6]

1. VAS patient's pain
2. CRP or ESR
3. Morning stiffness
4. Elevation of upper limbs (0–3)
5. VAS physician's global assessment
VAS pain + three performing best of no. 2–5 20%, 50%, 70%, 90% change from the baseline observation

assessment, CRP levels and MST, and the elevation of the upper limbs, showing the lowest degree of influence on the response rate. In view of the crucial role pain plays during the disease, it was decided to insist on the presence of a change of pain intensity, whereas out of the other four parameters, only three must change to indicate improvement or worsening of the disease (see Table 13.4). Thus, to achieve a 20% response rate, and a one of 50%, 70%, 90%, respectively, an amelioration of the VAS pain and three of the other four parameters is mandatory, whereby the lowest percentage change of one of the four parameters constitutes the threshold [6].

Applying these response criteria, 50% of the patients showed a 90% improvement in week 24, and the 70% response rate was at 76.8% [5]. No statistically significant differences could be found between the European and the Austrian patient cohort. When the individual response rates of the patients at the final control visit (week 33 mean) were compared with the rates at week 4, 20 patients had an identical or increasing response, while four patients (17%) showed a decrease of response, which are in line with the relapse rates for the international patient group. The measures particularly chosen to be part of the response criteria core set proved their sensitivity to change throughout the observation period [6].

Monitoring disease activity in daily practice and its documentation needs to be easy to perform and not time-consuming. Moreover, it should provide the physician with enough information to enable decision-making in treatment [16]. As criteria based on percentage changes from baseline may cause difficulties in daily practice, which is well known for the ACR response criteria for rheumatoid arthritis [13], it was considered useful to develop a simple disease activity index for PMR. Such an index, reflecting disease activity with an absolute number, would provide advantages with respect to comparability of patients and the lack of the need for a baseline observation to assess the patient's disease actual activity [16].

Based on the core set of parameters of the PMR response criteria, the disease activity index for PMR, the PMR-AS, was developed applying an easy-to-calculate formula:

CRP (mg/di) + MST (min) × 0.1 + possibility of elevation of the upper limbs (3 = none, 2 = below-shoulder girdle, 1 = up-to-shoulder girdle, 0 = over-shoulder girdle) + VAS patient's pain (0–10 cm) + VAS physician's assessment (0–10) = PMR-AS (see Table 13.5).

Cronbach's alpha, as a marker for reliability for composite scores, amounted to 0.914 and 0.881 in two patient cohorts, indicating high internal consistency. For

Table 13.5 Polymyalgia Rheumatica Disease Activity Score (PMR-AS) [16, 18]

CRP (mg/dl) + VAS patient's pain (0–10) + VAS PhAss (0–10) + [MST (min) × 0.1) + elevation of upper limbs (EU L; 3-0) = PMR-AS (0 = above-shoulder girdle, 1 = up-to-shoulder girdle, 2 = below-shoulder girdle, 3 = none)
• Emission (proposal) <l.5
• Low disease activity <7
• Medium disease activity 7–17
• High disease activity >17

individual analyses, a value >0.8 is regarded sufficiently valid [18]. Factor analysis by principal component analysis revealed that each single item of the PMR-AS contributes significantly to the total score. Moreover, the relative weight of the single items in both patient cohorts-the pan-European and the Austrian-was seen to be equally distributed. To evaluate whether the PMR-AS corresponds to ESR and patient's global assessment-hitherto the gold standard of monitoring PMR patients-a third independent patient cohort was assessed. A highly significant relationship of the new composite index and those parameters could be proven ($p < 0.001$) [16].

Additionally, a comparison of responses calculated based on the PMR response criteria and the PMR-AS applied and gave congruent results. PMR-AS values below 7 can be regarded as indicating low disease activity, between 7 and 17 medium disease activity, and greater than 17 high PMR activity [19]. As a further development, it was possible to define a value <1.5 as the threshold for a remission-like state of PMR using patient-relevant parameters such as pain assessment and satisfaction with disease status as benchmarks [18]. Meanwhile studies support the validity of PMR-AS in primary care practice and provide evidences that a good scoring system can be useful to guide clinical and therapeutic decisions. In addition, there is a new evidence that the PMR-AS is useful for monitoring PMR activity in everyday practice and for managing glucocorticoid tapering. In this respect, PMR activity changes as expressed by the PMR-AS seem even more relevant than absolute values [19, 20].

Thus, the PMR-AS provides an easily applicable and valid tool for disease activity monitoring in patients with PMR either in clinical trials or in daily routine as it also proved to mirror patients' satisfaction with disease status [14]. If used in combination with the EULAR PMR response criteria, a better description of response in the evaluation of new therapies will be possible [16]. Meanwhile the PMR-AS proved to be a reliable tool for disease activity assessment in clinical trials, primarily with tocilizumab, as well as in daily practice, and can be regarded a reference parameter [21].

In patients with GCA, improvement of systemic symptoms (e.g., headache, lethargy) typically occurs within 72 h of initiation of therapy. The elevation in erythrocyte sedimentation rate (ESR) and ischemic manifestations (e.g., temporal headache, jaw claudication) diminish in several days. The ESR often drops even in patients with a normal baseline reading. Patients with multi-infarct dementia from GCA should not expect immediate cognitive recovery; however, longitudinal follow-up should show no further deterioration and may show modest improvement. Even with prompt treatment, visual loss may be permanent [9, 22, 23]. Steroids should be

tapered slowly to the lowest dose required to suppress symptoms. Both clinical signs and sequential measurements of the ESR (or CRP level) assist in monitoring the patient's response. Patients with visual involvement usually require slower tapering of corticosteroids. Once the signs of clinical inflammation are suppressed and the ESR is maintained at a low level, corticosteroids may be tapered in almost all patients, and the steroid dosage can be significantly decreased; however, the inflammatory process may ebb and flow, and temporary dose increases may be needed to control disease flares. Relapse occurs in 25–60% of cases [23].

The dose of prednisone should be increased only if clinical manifestations recur, and not simply based on an elevation of the ESR. An elevated ESR without accompanying symptoms or signs of GCA could be related to an infection. No absolute guideline exists as to the length of treatment with corticosteroids for GCA [22], nor a core set of monitoring parameters, except the acute phase response parameters. In most clinical trials, clinical remission is defined as an ESR less than 40 mm in the first hour and lack of the symptoms or signs of GCA. Complete clinical remission was defined as maintenance of clinical remission for 12 weeks after discontinuation of glucocorticosteroid therapy [24].

It may be reasonable to maintain the patient on treatment for 2 years to lessen the chances for relapses. Imaging tests may be used for diagnosing giant cell arteritis as well as for monitoring the treatment response. Possible tests include:

- *Magnetic resonance angiography (MRA)*. This test combines the use of magnetic resonance imaging (MRI) with the use of a contrast material that produces detailed images of your blood vessels. Let your doctor know ahead of time if you're uncomfortable being confined in a small space because the test is conducted in a tube-shaped machine [21].
- *Doppler ultrasound*. This test uses sound waves to produce images of blood flowing through your blood vessels [22].
- *Positron emission tomography (PET)*. Using an intravenous tracer solution that contains a tiny amount of radioactive material, a PET scan can produce detailed images of your blood vessels and highlight areas of inflammation [23].

13.2 Complications During Treatment

Despite all the knowledge about the overwhelming beneficial effects of corticosteroid treatment of PMR, data concerning the optimal dosage regime are lacking. Long-term corticosteroid use can be associated with various adverse events, with the induction of osteoporosis, diabetes, hypertension, or infection among the worst [25]. Therefore, monitoring of blood sugar levels, body weight, and blood pressure in regular intervals is mandatory [26].

Supplementation of calcium and vitamin D should be initiated along with corticosteroids, osteodensitometry performed to estimate the respective risk, and bisphosphonates applied, if needed [25].

It is necessary to emphasize that adverse effects may outweigh the beneficial effects of corticoid treatment. A safe prednisone dose with no risk for the development of osteoporosis has not been determined yet; however, daily prednisone doses below 5 mg can be considered relatively safe. Another aspect is that osteoporosis is known to be promoted by general inflammation. Therefore, the question whether corticosteroids decrease bone mass in PMR patients or even increase it by reducing the inflammatory activity should be addressed in future investigations [25]. In any case, the patients should be monitored closely, including densitometry and laboratory parameters.

As PMR constitutes a disease preferentially affecting the elderly, the risk of developing diabetes mellitus in this population is obviously increased compared to younger people. It is regarded as one of the main risks of prolonged corticosteroid therapy to eventually promote the development of diabetes, even though only a few clinical data concerning the likelihood of promoting diabetes by corticosteroids are existing [27, 28]. Therefore, a serious risk evaluation in PMR patients is of high interest as it might be corticosteroid dose dependent or influenced by the duration of therapy.

In addition to the risk of promoting diabetes mellitus and osteoporosis, blood pressure increase, a higher risk of infections, the worsening of a cataract, and muscle weakness can be considered other important undesirable adverse events due to corticosteroids [28]. All those side effects due to the application of corticosteroids are well known; however, in the literature, not much information about the prevalence of these adverse events could be found. Aside from the objective risks of corticoid therapy, some other unpleasant side effects may interfere with the patients' well-being. To quantify these primarily subjective side effects, a questionnaire—the so-called SCSEQ (Stockerau Corticosteroid Side Effect Questionnaire)—consisting of seven to eight questions with yes or no answers, was developed (see Table 13.6) [28]. This

Table 13.6 The Stockerau Corticosteroid Side Effect Questionnaire (SCSEQ) [28]

1. Do you think that the new drug alters your mood?	
Yes	No
2. Do you feel depressed?	
Yes	No
3. Do you think of having more infections, like common colds, since you take the new drug?	
Yes	No
4. Did your body weight increase?	
Yes	No
5. Do you need higher doses of antihypertensive drugs than before taking the new drug?	
Yes	No
6. Do you suffer from alterations of the skin?	
Yes	No
7. Do you suffer from muscle weakness?	
Yes	No
8. Do you suffer from alterations of the menstruation cycle?	
Yes	No

questionnaire proved to be able to discriminate between corticosteroid users and non-users and in addition revealed a significant relationship between the daily corticosteroid dose and number of positive answers. The patient-relevant adverse effects most frequently quoted by corticosteroid users were mood change, weight gain, and muscle weakness [28].

Conclusion

Polymyalgia rheumatica and giant cell arteritis are related diseases with systemic as well as local manifestations [29]. Delayed diagnostics and treatment may be of serious and even lethal consequences for a patient. Arteritis of cerebral or extremity vessels resulting in stenosis or occlusion and aortic arteritis may result in dissection or rupture, especially in elderly patients. Early diagnosis of the disease, appropriate treatment, and life-long monitoring of GCA patients may prevent serious complications, such as loss of vision, myocardial infarction, dissecting aortic aneurysm, or critical lower extremity ischemia and amputation. Moreover, it is important to emphasize that PMR and GCA may also occur in younger patients and with only slightly elevated inflammatory reactants and varying disease localizations [27, 29].

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The Risk of Venous Thromboembolism in Giant Cell Arteritis

14

Denisa Čelovská and Viera Štvrtinová

14.1 Introduction

Giant cell arteritis (GCA) is a frequent form of vasculitis in adults characterized by systemic immune-mediated granulomatous inflammation of the large- and medium-sized arteries [1]. The first clinical description of giant cell arteritis was presented by Hutchinson in 1890 [2]. In 1930 Horton and colleagues described the histologic appearance of granulomatous arteritis of the temporal vessels [3]. The relation between polymyalgia rheumatica (PMR) and giant cell arteritis was not widely accepted. Paulley and Hughes were among the first to recognize the association [4]. Other names for GCA include temporal arteritis, arteritis cranialis, Horton disease, granulomatous arteritis, and arteritis of the aged. Nowadays, GCA as large vessel vasculitis is the preferred term according to the second International Chapel Hill Consensus Conference 2012 (CHCC 2012) [5].

Giant cell arteritis and PMR can be regarded as quite rare systemic inflammatory diseases in the general population; however, their incidence increases with increasing age, and it may be anticipated that those disorders are frequently under-recognized [6]. GCA occurs primarily in patients older than 50 years, in women more than in men, and in the whites. PMR and GCA are particularly uncommon in African Americans. The frequency varies according to country, with the highest rates occurring in the Scandinavian countries, with the annual incidence of 20–25/100,000 inhabitants. In Germany the annual incidence reaches approximately 3.5/100,000 inhabitants [7].

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14.2 Etiology and Pathophysiology of GCA

The etiology of GCA is unknown. In genetically predisposed patients, the disease may be triggered by environmental factors such as viruses; *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Helicobacter pylori* infection; or internal antigens such as elastin. Inflammatory manifestations are directed by cell-mediated Th_1 immune mechanisms [1, 8].

The adventitia is considered to be the immunologic center in the pathogenesis of GCA. Macrophages and T lymphocytes enter the vessel wall through the vasa vasorum. Clonal proliferation of $CD4^+$ T cells is triggered by unknown antigens. The activated CD4 cells produce interferon-γ that attracts macrophages to the arterial wall. Some of these macrophages fuse at the intima-media to form multinucleated giant cells. These cells produce vascular endothelial growth factor, which triggers neovascularization both in the intima-media junction and at the level of the vasa vasorum. The production of proinflammatory cytokines leads not only to the characteristic medial damage but also to the significant intimal hyperplasia that may cause luminal narrowing and tissue ischemia. GCA tissue contains the T-lymphocyte products interferon-γ and interleukin (IL)-2 and the macrophage products IL-1β, IL-6, and transforming growth factor-β. Patients with GCA, who present with fever of unknown origin and who do not have ischemic symptoms, have low interferon-γ levels. Arteries that express high interferon-γ levels typically have multinucleated giant cells present. These cells secrete cytokines that stimulate intimal hyperplasia and lead to angiogenesis [1, 8].

In GCA, a segmental transmural inflammatory process is involving all layers of the vessel. In elderly patients, fragmentation of the internal elastic membrane is characteristic and helps differentiate this vascular lesion from that of atherosclerosis [1]. GCA can result in a wide variety of systemic, neurologic, and ophthalmologic complications. Involvement of large vessels in GCA patients may result in fatal consequences [8, 9]. The process is highly responsive to corticosteroids. Association with atherothrombotic events is well known, while the risk of venous thromboembolism is underestimated. The role of thromboprophylaxis is still debatable. Studies are mostly focused on arterial events.

14.3 Clinical Manifestations, Diagnosis, and Treatment of GCA

GCA involves the aorta and its branches of the external carotid, especially the extracranial branches. Initial symptoms include new-onset persistent headache, scalp pain, jaw claudication, tongue pain on chewing or talking, and visual disturbances. Constitutional manifestations, such as fatigue, malaise, fever, and weight loss, may also be present. Temporal artery tenderness, nodularity, and diminished pulsation are typical findings during physical examination in a patient with GCA [1, 9]. GCA should always be considered in the differential diagnosis of a new-onset headache in older patients with an elevated erythrocyte sedimentation rate [10]. Some veins may be affected occasionally.

Ocular complications in GCA are diplopia, amaurosis fugax, fixed vision loss, and blindness. Initial visual symptoms are usually transient and intermittent, typically consisting of unilateral visual blurring or vision loss [8]. Alternatively, a partial field defect may progress to complete blindness over days. Fixed or intermittent symptoms related to vasculitic involvement of the ophthalmic arteries demand immediate therapeutic intervention. The visual disorder may be caused by a mixture of many ischemic events in the optic nerve, the extraocular muscles, and the brain itself. The most common cause of vision loss in GCA is anterior ischemic optic neuropathy (AION). This results from ischemia of the optic nerve head, which is supplied mainly by the posterior ciliary arteries [1, 8]. As GCA primarily involves arteries that contain elastica and the elastic lamina is lost as vessels pierce the dura, intracerebral lesions such as strokes are less common [8, 10].

Large artery involvement most commonly presents as arm or leg claudication; rarer manifestations are stroke, subclavian steal syndrome, intestinal infarction, and subclinical arteritis. Thoracic aneurysms with giant cells can develop as long as 15 years after the diagnosis and successful treatment. Indeed, the incidence of thoracic and aortic aneurysms is markedly higher in patients with prior history of presumably successfully treated GCA than in age-matched control subjects. Conversely, in studies of repaired aortic aneurysms, pathologic findings consistent with GCA have been found in approximately 2% of individuals without previously recognized or suspected arteritis [1, 8, 9].

The involvement of the coronary arteries in GCA patients is rarely recognized [11]. Patients with GCA have lower cholesterol level at the time of the diagnosis. Inflammatory process and corticosteroid therapy may however influence cholesterol levels [11]. Myocardial infarction may be a more common early complication of temporal arteritis than recognized and can occur despite administration of high-dose corticosteroid therapy [12]. Inflammatory affection of the coronary arteries may present a life-threatening factor. Since the epicardial coronary arteries are not easily accessible to biopsy, diseases involving the coronary arteries are rarely diagnosed correctly during the lifetime of the patients. However, a correct and timely diagnosis has become vitally important not only for the necessity to aggressively manage some “malignant” forms of vasculitis by immunosuppressive therapy but also because the needless administration of such therapy may lead to serious complications and adverse effects. It is therefore rather crucial to make an early distinction between vasculitis and atherosclerotic alterations since the management of the two conditions would be approached differently [11].

Diagnosis of GCA is based on clinical symptoms and signs, laboratory tests, diagnostic imaging methods, and temporal artery biopsy. The laboratory hallmark of GCA is an elevation in acute phase reactants such as the erythrocyte sedimentation rate (ESR) and the C-reactive protein. ESR is usually more than 50 mm/h and may exceed 100 mm/h. Normocytic, normochromic anemia and thrombocytosis occur. In GCA, the frequency of rheumatoid factor, antinuclear antibody, complement levels, monoclonal proteins, and cryoglobulins is not higher than in age-matched control subjects. Alkaline phosphatase activity may be elevated in one third of patients, primarily with GCA [1, 8].

Color duplex ultrasonography is a useful noninvasive diagnostic tool. A hypoechoic halo around the superficial temporal artery has been reported in 73% of patients with biopsy-proven GCA. Fluorodeoxyglucose-positron emission tomography may be helpful in identifying large vessel inflammation suggestive of GCA. Temporal artery biopsy remains the diagnostic "gold standard" in GCA [1, 8].

In a patient in whom the clinical diagnosis is likely, treatment with glucocorticoids should be instituted immediately without waiting for the biopsy results. Biopsy may be normal because of the skipped nature of the pathologic inflammatory lesions in the vessel wall. Patients with pure PMR and no GCA signs or symptoms do not need a biopsy. Prompt initiation of treatment may prevent blindness and other potentially irreversible ischemic complications. Corticosteroids are the standard therapy. In steroid-resistant cases, drugs such as cyclosporine, azathioprine, or methotrexate may be used as steroid-sparing agents. Typically GCA is high steroid responsive in a few days. Therapy lasts 2 years in most patients to avoid relapse. However, a subgroup of patients could have an active inflammation for several years [1, 8].

In most studies, survival time in GCA is similar to that of the general population of the same age. However, studies showed that survival time was decreased in a group of patients with GCA that had permanent visual loss, required high-dose corticosteroids for a long time, or have thromboembolic event [1, 8, 13]. This probably supports the hypothesis that the morbidity and mortality are caused by steroid-related treatment complications in this high-risk, elderly group of polymorbid patients.

14.4 Our Group of Patients

A total of 27 patients with GCA, 21 female and 6 male, with average age 71 ± 9.7 years were enrolled. The aim of our study was to evaluate the risk of VTE in patients with GCA and to determine the risk factor profile.

A total of 77.7% of GCA patients had diabetes mellitus or impaired glucose tolerance and 92.6% arterial hypertension, and 14.8% were active smokers. These were compared to 30 control patients without history of any cardiovascular event, being of similar age and sex. All patients were without previous history of VTE, cardiovascular event, or cancer. Data concerning potential risk factors (RF) were collected as varicose veins, arterial hypertension, smoking, diabetes mellitus, and dyslipidemia. For the baseline characteristics of GCA and control patients, see Table 14.1.

The diagnosis of DVT and superficial vein thrombosis (SVT) was established using Doppler ultrasonography. All patients in the VTE group received compressive stockings, anticoagulation therapy with low molecular weight heparins (LMWH) followed by oral anticoagulants for 6 months. Direct novel oral anticoagulants (NOACs) were not used. Patients with extended SVT more than 5 cm were treated with fondaparinux for 45 days.

Table 14.1 The baseline characteristics of patients with and without giant cell arteritis

	GCA	Non-GCA
Total of patients, *n*	27	30
Age (years)	71 ± 9.7	65 ± 10
Female/male	21/6	20/10
Arterial hypertension (*n* %)	92.6	90.0
Diabetes mellitus, IGT (*n* %)	77.7	50.0
Smoking (*n* %)	14.8	16.6
Dyslipidemia	59.2	54.0
BMI (kg/m^2)	32.0 ± 3.5	28.5 ± 3.2
Polymyalgia rheumatica (*n* %)	55.5	0
Varicose veins (*n* %)	29.6	33.3

GCA giant cell arteritis, *IGT* impaired glucose tolerance, *BMI* body mass index

Table 14.2 EULAR (European League Against Rheumatism) and ACR (American College of Rheumatology) classification criteria

• Age over 50 years
• New onset of localized headache
• Abnormality of temporal artery
• Raised erythrocyte sedimentation rate (ESR ≥ 50 mm/first hour)
• Abnormal arterial biopsy

Three criteria for the classification of GCA must be fulfilled

The relationship between GCA and risk of VTE was evaluated. Clinical and laboratory data were collected retrospectively. All patients met the EULAR (European League Against Rheumatism) and American College of Rheumatology criteria of GCA (Table 14.2) [5, 14].

We established diagnosis according to clinical symptoms and signs and laboratory and diagnostic imaging tests. Biopsy was performed only in ten patients. Typically GCA is high steroid responsive in a few days. Patients were absence of pulses on the temporal artery; presence of nodules, thickening, swelling, or tenderness on palpation; upper limb artery involvement; absent or decreased radial pulse; presence of intermittent arm claudication; and recent onset of Raynaud's phenomenon, suggestive findings on duplex ultrasound, selective aortic arch arteriography, or positive PET. Inflammatory markers including the erythrocyte sedimentation rate and levels of C-reactive protein, fibrinogen, platelets, mean platelet volume (MPV), and red distribution width (RDW) were used. We observed the erythrocyte sedimentation rate more than 50 mm/first h and C-reactive protein more than 25 mg/L. D-dimer was often false positive in patients without VTE. The mean value of fibrinogen was 4.7 g/L, MPV 9.7 fL, RDW 16%, and platelets 459 10^9/L in GCA group.

14.5 Our Study Inclusion Criteria Were

- Age over 50 years
- International classification of GCA code by rheumatologist or hospital GCA code no more than 2 years old
- Prescription of glucocorticoids

The following treatment was used in our group of patients. Prednisone was initiated 1 mg/kg/daily in GCA patients. Patients with ischemic symptoms received pulse intravenous methylprednisone (500–1000 mg daily for 3 days). When inflammatory and clinical markers fell down, prednisone was reduced progressively within 4–6 weeks. Glucocorticoid therapy at least 10 mg daily lasts 2 years in most patients.

Among 27 patients with GCA, 1 developed proximal deep vein thrombosis and 3 superficial vein thrombosis (SVT) during 2 years of retrospective study. SVT has been considered a relatively benign disease for a long time. However, more recent studies suggest that in quite a number of cases SVT may be accompanied by DVT and/or pulmonary embolism. Especially in cases of extensive SVT, anticoagulant therapy is a good choice. A total of 21 patients were treated with low-dose aspirin; 6 had sulodexide. Varicose veins were present in 29.6% of GCA patients and 33.3% of non-GCA patients. All of the GCA patients were treated with low-dose corticosteroids; 25.9% had COX-2 inhibitors. In the control group there was no VTE event. We compared baseline characteristics between GCA patients and the control group (Table 14.1). Statistical analyses were performed to compare GCA group and non-GCA group using χ-square test, $p = 0.042$. The risk of VTE was the highest during the first 3 months after initiation of glucocorticoid therapy in our study (Fig. 14.1).

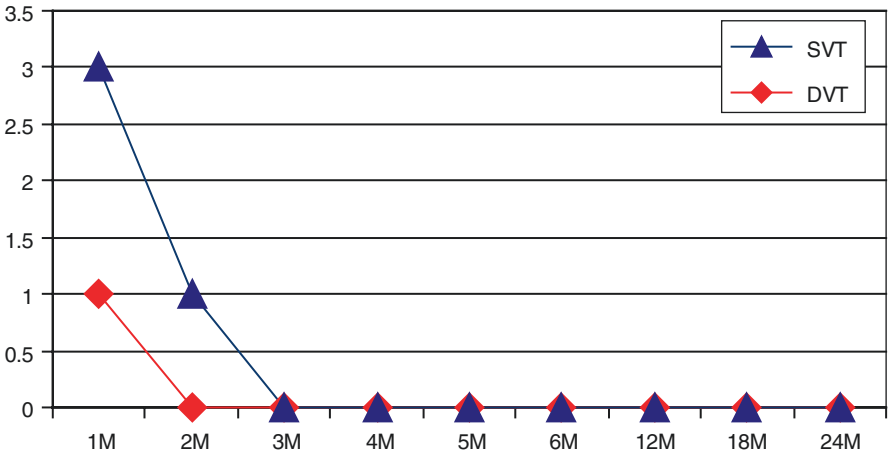

Fig. 14.1 Increased risk of venous thromboembolism after initiation of corticosteroid therapy in giant cell arteritis. *DVT* deep vein thrombosis, *SVT* superficial vein thrombosis, *M* month. $p = 0.042$, χ^2 test

14.6 Giant Cell Arteritis and Venous Thromboembolism

Patients with GCA may have an increased risk of venous thromboembolism, similar to other systemic vasculitides. However, no relevant population data are available. We have confirmed that GCA is associated with increased risk of VTE. The increased risk was the highest during the first 3 months after initiation of the corticosteroid therapy in our study. Treatment of GCA patients with low-dose aspirin is already routine practice to prevent ischemic events. It is evident that the optimal thromboprophylaxis needs more investigation in the future in GCA patients. Several mechanisms could be involved in the increased risk of VTE. Virchow's triad—stasis, hypercoagulability, and endothelial damage—are key factors. Advanced age together with cardiovascular (CV) risk factors, decreased mobility, inflammation, and glucocorticosteroids (GCs) contributes to increased thrombotic risk. Systemic inflammation in GCA may modulate thrombotic response [1, 8, 10].

An increased risk of the VTE was recently reported in patients with GCA with incidence rate ratio (IRR) of 3.58 (Table 14.3) [15]. The risk of VTE in GCA group was the highest in the first year of GCA diagnosis (Table 14.4) [15].

One study showed increased odds ratio for DVT of 2.08, delirium, and adrenal insufficiency in patients with GCA [16]. The aim of a Canadian Observational Cohort study of general population of British Columbia was to evaluate the future risk and time trends of new VTE in individuals with GCA at the general population level. A total of 909 patients with GCA and 9288 age-matched, sex-matched control patients without a history of VTE were studied. Among 909 individuals with GCA (mean age 76 years, 73% of women), 18 developed PE and 20 developed DVT (Table 14.3) [15]. These findings provide general population-based evidence that patients with GCA have an increased risk of VTE, calling for increased vigilance in preventing this serious, but preventable complication, especially within months after GCA diagnosis [15].

However, these epidemiologic studies did not provide data regarding GCA presentation and outcomes in patients with GCA who developed VTE. Inception cohort study including 428 newly diagnosed patients of giant cell arteritis was performed from 1976 to 2014 with biopsy-proven GCA. In the study VTE was observed in 6% patients with GCA [13]. Clinical and biological data and outcomes were analyzed

Table 14.3 Risk of incident of venous thromboembolism in patients with giant cell arteritis [15]

	GCA n 909	Non-GCA n 9258
VTE	31	121
PE	18	63
DVT	20	73
Incidence rate/1000 person—years VTE	13.3	3.7
Incidence rate ratio (95% CI)	3.6 (2.33–5.34)	1

VTE venous thromboembolism, *PE* pulmonary embolism, *DVT* deep vein thrombosis, *GCA* giant cell arteritis

Table 14.4 Time trends of incident rate ratios for VTE according to GCA duration [15]

	IRR (95% CI)		
Time after diagnosis	VTE	PE	DVT
1 year	7.03 (3.78–12.73)	7.23 (2.90–17.20)	7.85 (3.53–16.94)
2 years	4.98 (2.87–8.38)	5.20 (2.39–10.68)	5.44 (2.58–10.91)
3 years	4.34 (2.66–6.90)	4.66 (2.32–8.88)	4.07 (2.10–7.48)
4 years	4.09 (2.56–6.34)	4.21 (2.17–7.72)	4.27 (2.35–7.43)
5 years	3.69 (2.37–5.60)	4.09 (2.22–7.19)	3.92 (2.25–6.56)
Total follow-up	3.57 (2.33–5.34)	3.98 (2.2–6.8)	3.82 (2.20–6.34)

DVT deep vein thrombosis, *GCA* giant cell arteritis, *IRR* incidence rate ratios, *PE* pulmonary embolism, *VTE* venous thromboembolism

by comparing patients with and without venous thrombosis. The mean age at the time of diagnosis was 75.0 ± 7.8 years; 64% of the patients were female. Twenty-six patients (6%) developed venous thrombosis, 12 of whom presented with pulmonary embolism. A total of 14 patients (54%) had DVT, and 8 patients had both DVT and PE (31%). A previous history of VTE or varicose veins was significantly more common in patients with VTE (15% vs. 17%, $p = 0.0003$). Malignancy was observed in six patients with VTE. The mean time between onset of GCA and VTE occurrence was 248.8 ± 215 days, median 146 days. At the time of VTE, the mean C-reactive protein was 24.9 ± 27 mg/L (data available—10 patients). No difference was observed between the two groups in clinical or laboratory data collected at diagnosis. The mean time from the start of prednisone to venous thrombosis diagnosis was 187.7 ± 217.0 days. The average dose of prednisone at venous thrombosis onset was 21.5 mg/day. The venous thrombosis group had a higher number of glucocorticoid-related adverse effects (mean, 3.1 vs. 1.1; $p < 0.0001$), a higher mortality rate (58% vs. 33%, $p = 0.01$), and a higher proportion of deaths occurring during glucocorticoid treatment (31% vs. 14%, $p = 0.03$). VTE group developed more GC-induced diabetes (36% vs. 17.5%, $p < 0.05$) and GC-induced infections (44% vs. 23.7%, $p < 0.05$). Death was related to venous thrombosis in four patients [13]. VTE did not occur at the time of diagnosis of GCA but about 8 months after the onset of GCA and 6 months after corticosteroid initiation [13].

Some autoimmune diseases are associated with an increased risk of VTE compared with general population [17]. This association was found in patients with immune thrombocytopenic purpura, systemic lupus erythematosus and polyarteritis nodosa, etc. VTE is more frequent in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis than in those with polyarteritis nodosa [1, 8, 17]. Antiphospholipid antibodies may play a potential role in the risk of VTE, too. Among patients with large vessel vasculitis, only data for GCA are available.

Arterial hypertension was a potential risk factor (RF) for VTE in the GCA group in a general population-based study [15], but this finding could have been caused by the higher proportion of corticosteroid use in this group. Some authors suggest that the systemic inflammation associated with GCA is not a causal factor of VTE [13]. The role of glucocorticoids as a potential RF for VTE is controversial.

The relationship between glucocorticoid (GC) exposure and the risk of VTE has been investigated in patients with SLE, in which a higher mean daily GC dose was associated with VTE [18].

Glucocorticoids in the initial phase of treatment are risk factors for venous thrombosis; in long-term therapy, they are responsible for arterial thrombosis [19, 20]. GCs have an important role in regulation of vessel tone by inducing reduction of endothelial NO and synthesis of prostacyclin [20]. Glucocorticoid-induced hypercoagulability could explain this increased risk of VTE. A study of 24 healthy men who were randomly assigned to receive dexamethasone 3 mg twice daily or placebo for 5 days showed increase in clotting factor and fibrinogen level in dexamethasone group [21]. Systemic inflammation in GCA may modulate thrombotic response. Thrombocytosis commonly occurs in activated GCA. Not only platelet numbers but also platelet size measured as the mean platelet volume is considered to be indicators of platelet activity and possible predictors of thrombotic events in patients [22]. In our study, fibrinogen, mean platelet volume (MPV), and red distribution width (RDW) were significantly higher in GCA than in non-GCA patients. As VTE may be associated with increased mortality risk in patients with GCA, high index of suspicion should be applied in appropriate settings [23, 24].

One meta-analysis demonstrated a statistically significant increased risk of VTE among nonsteroidal anti-inflammatory drug users. Why NSAIDs may increase the risk of VTE is unclear. The pathophysiology of increased arterial thrombosis risk is explained by a thromboxane—prostacyclin imbalance. Inhibition of the COX-2 enzyme has been shown to inhibit the synthesis of prostacyclin, a potent platelet activation inhibitor, while stimulating the release of thromboxane, a potent platelet aggregation facilitator, from the activated platelets. This mechanism might explain the increased risk of venous thrombosis in this study. In fact, the VTE risk of selective COX-2 inhibitors appears to be higher than overall NSAIDs [25].

Treatment of GCA patients with low-dose aspirin (100 mg daily) is already routine practice to prevent ischemic events. Other ADP blockers as clopidogrel could be used, too. Sulodexide shows many biological pleiotropic actions indicating effectiveness in arterial, venous, and capillary disorders. Sulodexide provides restoration of damaged endothelial glycocalyx, as well as antioxidant, antithrombotic, antiproliferative, and anti-inflammatory activities [26]. Treatment of vasculitis should be based on established pathophysiological concepts. Inflammation and endothelial dysfunction play key roles in this process. Application of sulodexide could help to alleviate progress of the disease and prevent recurrent thrombosis. It is evident that the optimal thromboprophylaxis needs more investigation in the future in GCA patients. VTE prophylaxis generally is associated with a benefit for medically ill patients, if they do not have contraindication to therapy. Of great importance is minimizing the risk of bleeding in low-risk patients for VTE. Further studies to optimize the risk-benefit ratio are needed. In initial phase of GCA treatment, venous thromboprophylaxis is underestimated. Extended thromboprophylaxis is needed in patients with risk factors for venous thromboembolism such as history of previous VTE, varicose veins, decreased mobility, cancer, high systemic inflammatory activity, and high-dose glucocorticoid therapy. Anticoagulation

therapy in therapeutic dose is indicated in all cases of venous thromboembolism and severe thrombophilia. Experience in direct novel oral anticoagulants is missing. Superficial vein thrombosis is no more a benign condition, especially non-varicose and extended SVT is calling for increased vigilance in preventing serious VTE complications. Gold standard of treatment remains compressive therapy and mobilization of all patients, even with vasculitis. In fact, the most important prophylactic approach in VTE may be avoidance or reduction of smoking, obesity, and estrogen-containing oral contraceptive pills and treatment of chronic venous disease.

Conclusions

- The risk of VTE in GCA patients increases especially after initiation of corticosteroids and within long-term high-dose steroid therapy.
- Advanced age together with CV risk factors, decreased mobility, inflammation, and corticosteroids contributes to increased thrombotic risk.
- Optimal thromboprophylaxis needs more investigation in the future in GCA patients.
- There should be increased vigilance by controlling the inflammatory process and prevention of glucocorticoid therapy-related complications.

Venous thrombosis may be associated with an increased mortality risk in patients with giant cell arteritis, especially in patients experiencing multiple glucocorticoid-related adverse effects [13, 23, 24]. Ultimately, global GCA therapy should focus on reduction or prevention of the disease- and treatment-related complications. There is evidence that patients with GCA have an increased risk of VTE. Therefore, there should be an increased vigilance in preventing this serious, but preventable, complication, especially within months after GCA diagnosis and initiation of glucocorticoid treatment.

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Temporal Arteritis and Polymyalgia Rheumatica: An Acute Condition in Rheumatology

15

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Temporal arteritis (TA), Horton's disease, is vasculitis of unknown etiology involving large blood vessels and external and internal carotid branches. It typically occurs in individuals older than 50 years and is 2–3 times more frequent in women than in men [1].

Histological findings show panarteritis, i.e., involvement of the whole arterial wall, which however is segmental, with pathologically altered sections of the artery alternating with those without pathological changes. It typically affects the temporal artery, but the most feared complication is involvement of the ophthalmic artery, leading to ischemia of the optic nerve with a high risk of irreversible loss of vision. Onset of the disease is gradual, with development of general symptoms such as weakness, subfebrility or even fever, loss of weight, and headache, often misinterpreted as flu symptoms. Headache occurring in three fourth of patients is intensive, chronic, and localized in the temporal and occipital areas, getting worse during hair combing. The temporal artery is usually swollen and tender, with reduced pulsation, and the patient has red patches on the scalp. Visual disturbance is found in 25–50% of patients in the form of decreased visual acuity, diplopia, scintillating scotoma, narrowing of the field of vision, and transient or complete loss of vision. Vision disorders are often unilateral [2].

In 1990, the American College of Rheumatology published classification criteria for TA diagnosis (ACR 1990), including:

1. Age at disease onset ≥50 years
2. New onset of or new type of localized pain in the head

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3. Temporal artery tenderness or decreased temporal artery pulse
4. Elevated ESR exceeding 50 mm/h
5. Positive histological finding in biopsy

TA diagnosis is established if three of five criteria are met [3].

Polymyalgia rheumatica occurs alone or in combination with temporal arteritis and also affects elderly population [4]. It manifests itself by pain and stiffness of the shoulder and pelvic girdles, as well as by morning stiffness. Simultaneous development of TA and PMR is associated with recurrent fever. Objective symptoms of a muscle disease are absent, i.e., absence of muscle enzyme positivity; EMG and histological findings are within standard. Laboratory tests typically show a high inflammatory activity, anemia, and thrombocytosis. PMR diagnosis is based on clinical features, as no examination is specific for this disease. The disease is characterized by a prompt clinical and laboratory response to corticoid treatment [5].

15.1 Case Reports

15.1.1 Patient 1

Patient's medical history: An 85-year-old woman with a positive family history. The patient's younger sister was treated for discoid lupus; the patient's daughter was followed up by neurologist for epilepsy and was examined also in the rheumatology outpatient department for positivity of ANA antibodies, but without a clinical correlation. From 1974, the patient was treated for ischemic heart disease. In July 2001, she was admitted to the Department of Neurology for a sudden loss of vision in the right eye and vertigo. Three weeks before that, she was examined by the general practitioner for persistent headaches, weakness, subfebrility up to 38 °C, and loss of appetite. The general practitioner established the diagnosis of flu and prescribed treatment with antibiotics—amoxicillin and spiramycin. During this treatment, the patient suddenly lost her sight on the third day.

Objective finding and results of examinations: The objective finding included asthenia, pale skin and mucous membranes, palmar erythema, and arcus senilis corneae. The temporal artery on the right was not visible due to a scar after operation of a basal cell carcinoma. Cardiopulmonary condition was compensated, blood pressure 115/80, and musical systolic murmur 3/6 in intensity over the aorta, radiating to carotids. Lower extremities showed symptoms of chronic venous insufficiency. The patient's gait was unsteady with a tendency to fall backward. Laboratory tests upon admission revealed three-digit ESR, mild anemia, elevated levels of fibrinogen, and other acute inflammation reactants (Table 15.1).

Autoantibodies—ANA, ENA, DNP, ANCA, and ACLA—were negative.

Eye examination: Eye fundus examination confirmed anterior ischemic optic neuropathy (AION) of the right eye.

Table 15.1 Lab test results prior to and after corticoid treatment

	Prior to treatment—July 2001	After treatment—August 2001
FW	100/120	5/20
Blood count—Hgb (g/L)	109	117
Htc	0.32	0.37
Lkc ($\times 10^9$/L)	10.3	14.0
Plt ($\times 10^9$/L)	335	206
Fibrinogen	6.57	2.84
AST (μkat/L)	1.9	0.6
ALT (μkat/L)	1.56	0.58

Radiological finding of the skull was normal; CT examination of the brain revealed only a minor ischemic focus in the midbrain on the left side and signs of cerebral atrophy of the cortical type.

Clinical features and laboratory parameters signaled diagnosis of giant cell vasculitis with involvement of the ophthalmic artery on the right.

Therapy: The patient was treated with prednisone at the dose of 80 mg/day in combination with vasodilation therapy. Due to the gastroscopy finding of numerous contact bleeding erosions in the region of the stomach, it was necessary to reduce corticoid doses more rapidly. During 3 weeks, the prednisone dosage was decreased to 30 mg/day. The patient's condition improved, she was afebrile, she stopped losing weight, and laboratory parameters returned to normal (Table 15.1). However, the vision was not restored. After 3 weeks, the patient was discharged to home care with the prednisone dosage of 30 mg/day, gastroprotectives, and a recommendation to reduce prednisone doses by 2.5 mg/week.

15.1.2 Patient 2

Patient's medical history: A 69-year-old woman without rheumatic diseases in the family history. The patient had a history of a hot nodule in the right thyroid flap, detected in 1984 and treated with carbimazole until 1992. In 2001, the patient overcame bilateral phlebothrombosis; in the same year, she was diagnosed with ischemic heart disease of NYHA I–II and complete BPTR on ECG record. In March 2003, the patient experienced gradually increasing pain and weakness of the shoulders and thighs and loss of appetite and weight.

Objective finding and results of examinations (March 2003—outpatient department): The objective finding was dominated by muscle hypotrophy, palpable small lymph nodes under the right mandible, and kyphoscoliosis. The patient's cardiopulmonary condition was compensated, with regular, slightly increased heart frequency and normal tension. Arthrological examination revealed slight tenderness of small joints of hands (PIP and MCP), elbows, and shoulders; reduced active range of motion of the shoulders due to pain; passive range of motion without limitation; and limited abduction of hip joints. Due to pain the patient was unable to bend her knees.

Laboratory tests showed repeatedly three-digit ESR, anemia, CRP positivity, and elevated fibrinogen levels.

In June 2003, the patient was admitted to the Department of Internal Medicine, where she underwent complete examination, which eliminated malignant disease as well as myositis; the EMG finding was normal, muscle enzymes were repeatedly within the standard range, and parainfectious cause of myalgia was excluded. The condition was classified as polymyalgia rheumatica.

Therapy: Treatment with prednisone started at the dose of 20 mg/day. During this treatment the patient's clinical condition improved and laboratory parameters returned back to normal. At the beginning of July 2003, the patient was transferred to outpatient care in a good condition. However, due to improvement, the patient willfully discontinued the treatment at the end of July.

In August 2004, the patient was readmitted to the Department of Internal Medicine for persistent headaches, weakness, fever, subfebrility up to 37.5 °C, and swelling of veins on both sides of the forehead. The objective finding upon admission included ropy segmental swelling in the area of the temporal artery, more marked on the right, and tender to palpation.

Laboratory tests revealed high ESR, mild anemia, mild thrombocytosis, elevated CRP levels, and negative rheumatoid factor. ANA autoantibodies were positive. Biopsy was performed in the area of the temporal artery with a subsequent histological confirmation of the suspected diagnosis of temporal arteritis. The histological finding included mononuclear inflammatory infiltrate and fragments of destructed internal elastic lamina.

Corticoids were added to the treatment at the dose of 50 mg/day together with H-blockers due to the patient's history of ulcerative disease.

During several days, the clinical condition improved, humoral activity decreased, and headache subsided. The patient was transferred to a geriatric center and subsequently discharged to home care and was treated in the outpatient department, with gradual reduction of prednisone dosage.

At the last follow-up in June 2005, she did not report headache; laboratory findings included FW 3/7, blood count within standard, negative CRP, and liver enzymes within the physiological range. Subjectively the patient complained of vision impairment and was referred to eye examination. She continues in the treatment with prednisone at the dose of 15 mg/day, receives famotidine, and is treated for ischemic heart disease.

15.2 Discussion

Temporal arteritis—isolated or in combination with polymyalgia rheumatica—poses a serious problem in terms of both diagnosis and treatment of the patients. Onset of the disease is gradual and the initial manifestations are nonspecific. Therefore, it is often misdiagnosed, most often as the flu, and, consequently, improperly treated. The disease affects usually elderly individuals with multiple comorbidities, in which it is necessary to exclude another inflammatory rheumatic disease,

or other nonrheumatic causes of myopathies, as well as oncologic diseases. The treatment must take into account adverse effects of corticosteroids and has to be often combined with a simultaneous gastroprotective therapy and treatment of osteoporosis. Early diagnosis and treatment of temporal arteritis is a basic prerequisite for preservation of the patient's sight.

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Giant Cell Arteritis, Polymyalgia Rheumatica, and Ocular Involvement

16

Jozef Rovenský and Igor Kozák

Giant cell arteritis (GCA) is a systemic granulomatous vasculitis of unknown etiology that typically involves the branches of the carotid artery (the temporal artery, in particular). However, it may affect any medium- or large-sized artery which makes establishment of its diagnosis even more difficult [1]. As early as in the tenth century, the famous Arabian physician Ali ibn Isa recommended removal of the temporal artery in order to treat migraine in patients with a simultaneous chronic eye disease often terminating in loss of sight [2]. From the clinical point of view, temporal arteritis was for the first time described by Hutchinson in 1890; the histopathological features related to the clinical syndrome were outlined by Horton in 1932, but it was as late as in 1938 that Jennings recognized that blindness might be a severe complication of the disease [3]. Later Gilmour, a pathologist, found out that temporal arteritis could involve also other arteries, and he was the first to use the term "giant cell arteritis."

GCA is a chronic inflammatory condition that primarily affects large- and medium-sized arteries. Clinical features comprise two different sets of symptoms, one indicating arteritis and the other polymyalgia rheumatica (PMR) that was for the first time described by William Bruce in 1888. Today it is clear that GCA is a systemic disease with a number of life-threatening cardiovascular complications. Its manifold and varying clinical presentation and course of the disease are probably caused by the heterogeneity of both immune and inflammatory response in individual patients [4]. GCA most frequently affects the branches of the carotid artery (the temporal artery), but actually it is a systemic granulomatous panarteritis that

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may involve any medium- or large-sized artery. The disease is sometimes referred to as temporal arteritis with the term "temporal" put into quotation marks to express a frequent, however not obligatory, involvement of the temporal artery. The temporal artery may be affected by a pathological process also in other forms of vasculitides, as, e.g., in Wegener granulomatosis or microscopic polyangiitis. On the other hand, inflammation of the temporal artery is not necessarily manifested in all patients with giant cell arteritis [5]. Temporal arteritis (i.e., arteritis involving the temporal artery) is not a lethal disease, with the mean longevity of the patients being the same as in the healthy population. However, giant cell arteritis involving large- and medium-sized arteries may have fatal consequences and is often dramatically manifested in the elderly by aortic dissection or rupture [6, 7] but also by myocardial infarction or stroke [8]. Unlike Takayasu's arteritis, GCA is a disease of the elderly, developing most frequently at the age over 50 years but quite often as late as at the age of 70–80 years. Recently reports were published also of so-called juvenile giant cell temporal arteritis [9, 10] confirmed by histology.

16.1 Incidence

In Minnesota (USA), the average annual incidence of the disease grew in 1970–1974 to 17.4 per 100,000 inhabitants older than 50 years from 5.1 in 1950–1959 [11]. This increase, however, may result also from improved diagnosis. In Göteborg the annual incidence of histologically confirmed GCA was 5.5 cases per 100,000 inhabitants or 16.8 cases when only inhabitants older than 50 years were taken into account [12]. In the UK, GCA incidence in 1990–2001 was on average 2.2 cases per 10,000 inhabitants annually and the incidence of polymyalgia rheumatica (PMR) 8.4 cases per 10,000 inhabitants [1]. Both PMR and GCA were more frequently diagnosed during summer months and more often in the south than in the north of the country. GCA is most common in Caucasians; in other ethnic groups, it is extremely rare. Women are affected about twice as often as men [13]. Their inflammatory response is more intensive, and the time to treat it is longer than in men [14]. A majority of data on the disease comes from the northern European countries and North America. The highest incidence of the disease has been recorded in the Scandinavian countries [15].

16.2 Etiology

Although the exact etiology is not known, genetic predisposition as well as autoimmune mechanisms take part in the development of the disease. Predominance of GCA in the Caucasian race, its increased incidence in certain families, and association with HLA-DR4 antigen support the genetic theory of this condition [2, 16]. It is assumed that a certain pathogenetic role is played by cellular immune mechanisms, as well as deposition of immune complexes. The patients exhibited increased IgG, IgA, and IgM serum levels, and immunofluorescence studies of the affected arterial walls showed deposits of immunoglobulins and complement. Macrophages,

epithelial cells, and giant cells in arterial lesions produce various adhesion molecules, including ICAM-1. These facts indicate that inflammatory response in GCA is the response of T cells to the antigen present in tissue macrophages [17]. Increased production was also observed of interleukin IL-1 beta and interferon gamma, which seems to be an important factor of modulation of hyperplasia of the intima of inflamed blood vessels. GCA is associated with an increased systemic concentration of interleukin IL-6, which decreases during glucocorticoid therapy, and is probably accompanied not only by activation of the vessel wall inflammation but also by systemic activation of monocytes [18].

Abrupt onset of the disease and the wide variation in incidence of GCA and PMR reported from various parts of the world suggest a potential influence of environmental factors. Olsson et al. [19] observed a higher incidence of both conditions during two epidemics of *Mycoplasma pneumoniae* infection. The seasonal incidence of PMR and GCA correlates also with epidemic spread of infections caused by *Chlamydia pneumoniae* and parvovirus B19 [20]. Another potential mechanism are seasonal changes in the immune system that make the organism more susceptible to various diseases [13].

In genetically predisposed individuals, pathogenetic factors may include also neuroendocrine changes induced by natural aging of the organism. However, monitoring of these changes is complicated by complex feedback relationships, and, in addition, the ongoing chronic inflammation modifies the neuroendocrine response. Patients with GCA exhibit an increased incidence of hypothyreosis. Antithyroid antibodies were found in about 10% of them [17]. Good response to glucocorticoid treatment supports the hypothesis that cortisol levels are lower in GCA patients. It is hypothesized that an important role in the pathogenesis of the disease is played also by changes in the endocrine system and the subsequent neuroendocrine response, which is confirmed by the fact that administration of glucocorticoids quickly suppresses inflammation [18, 21, 22].

16.3 Histopathology

One of the typical histopathological findings in GCA is a granuloma, or a focal inflammation of the media, as seen in Fig. 16.1 in the media of the abdominal aorta in an 86-year-old patient (hematoxylin and eosin (H&E) staining). Figure 16.2 shows a detail of an inflammatory infiltrate composed predominantly of histiocytes and plasma cells, not so many lymphocytes, and one giant multinucleated cell. In the area of the granuloma, the structure of elastic fibers disappears. All arterial wall layers are involved but most of them the media. The internal elastic lamina membrane is split and fragmented, as seen in Fig. 16.3. Figure 16.4 shows a detail of calcium powder in the area of the internal elastic lamina. Other histological images of the aorta of the same patient (Figs. 16.5 and 16.6) show typical multinucleated giant cells. Focal inflammation formed by giant cells involves only part of the blood vessel wall, the other parts of which exhibit smooth muscle atrophy of the media together with marked calcifications. Typical deposits of calcium salts in the aorta of an 84-year-old female patient are seen in the area of the internal elastic lamina

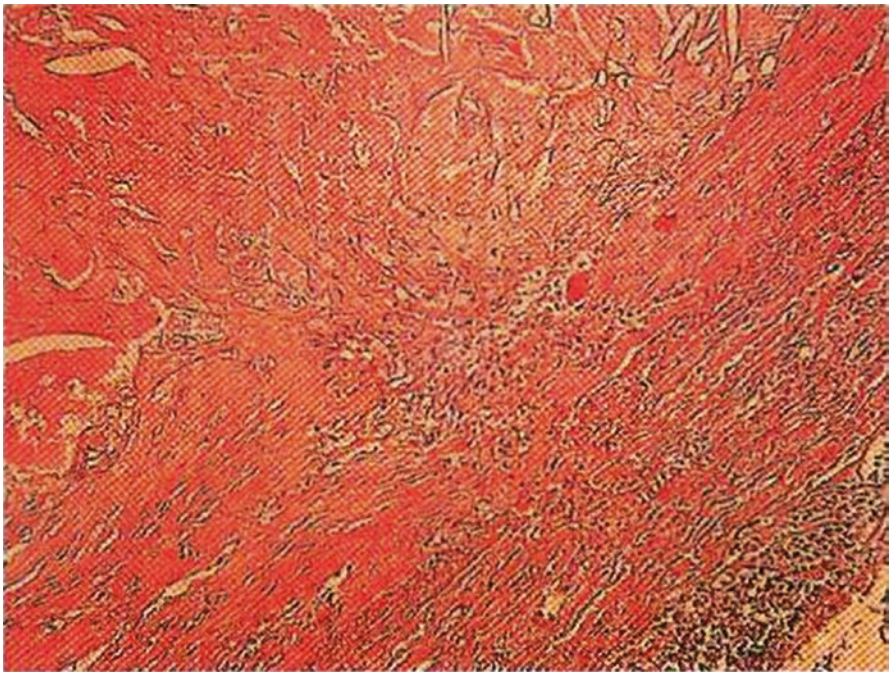

Fig. 16.1 Granuloma in the media of the abdominal aorta (hematoxylin and eosin (H&E) staining)

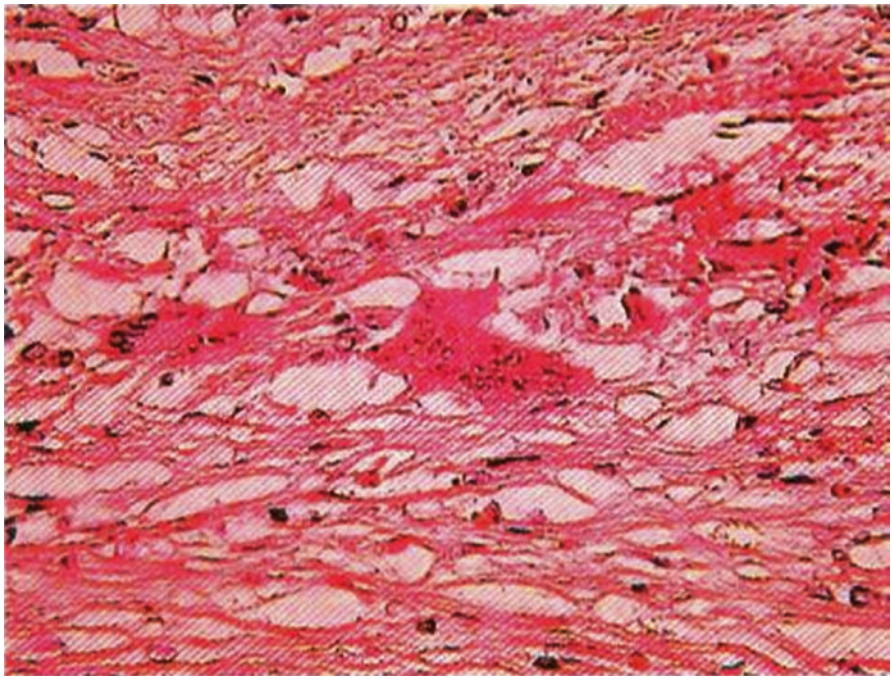

Fig. 16.2 Inflammatory infiltrate composed predominantly of histiocytes and plasma cells, not so many lymphocytes, and one giant multinucleated cell (hematoxylin and eosin (H&E) staining)

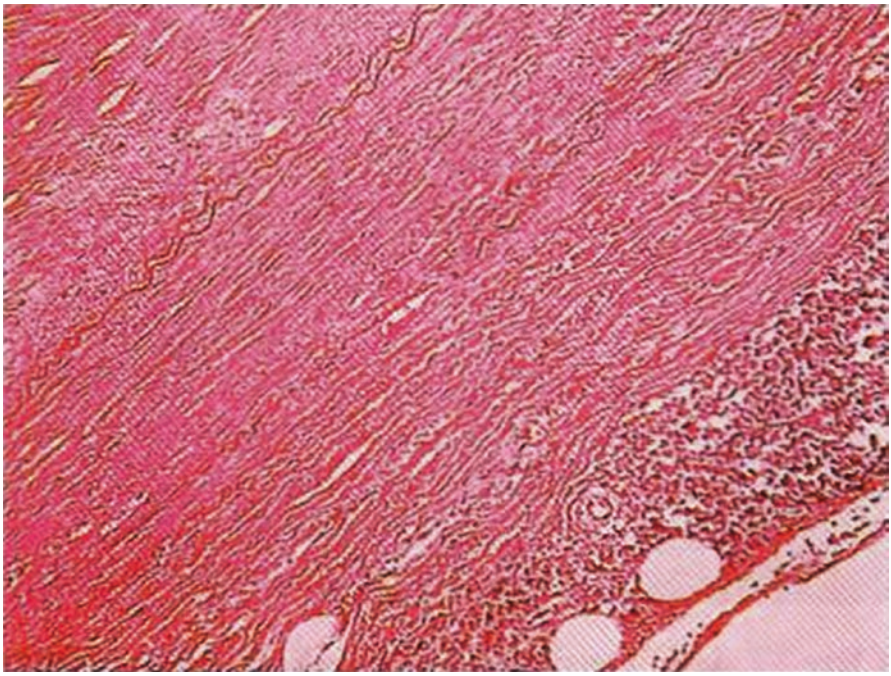

Fig. 16.3 Splitting and fragmentation of the internal elastic membrane (hematoxylin and eosin (H&E) staining)

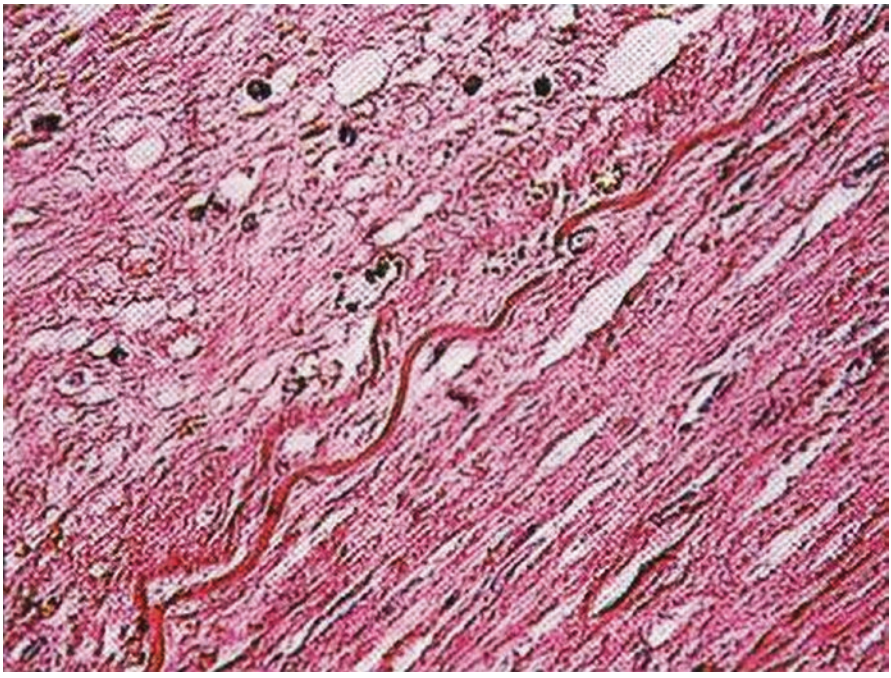

Fig. 16.4 Calcium powder in the internal elastic lamina

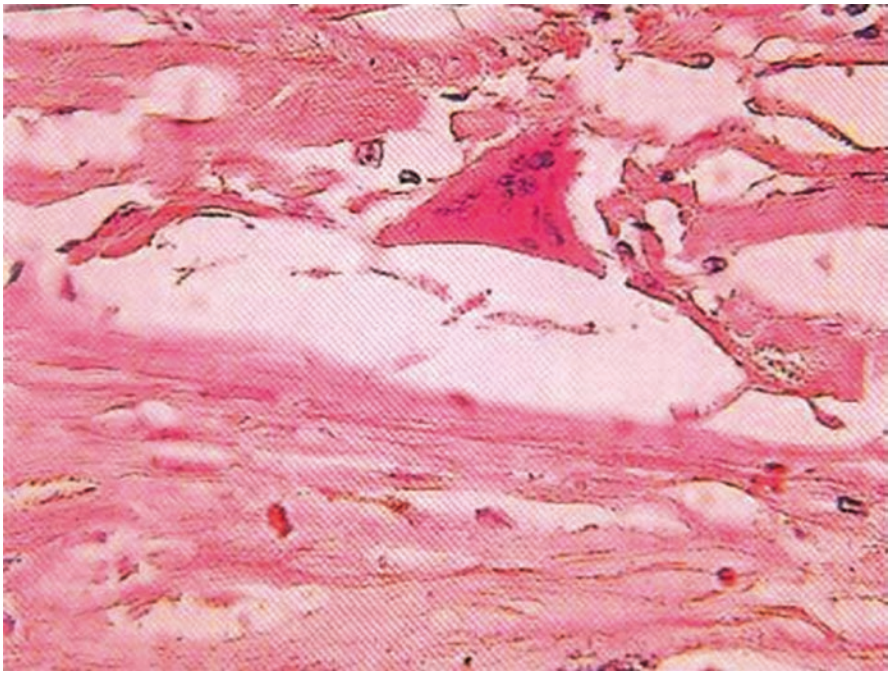

Fig. 16.5 A multinucleated giant cell. Aorta of an 86-year-old man (hematoxylin and eosin (H&E) staining)

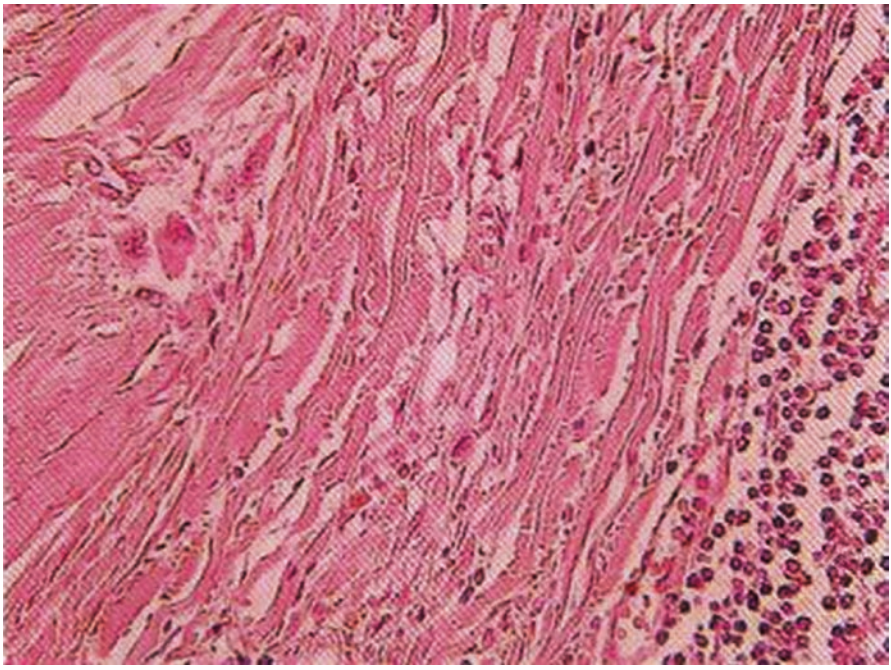

Fig. 16.6 Split internal elastic lamina. A multinucleated giant cell (hematoxylin and eosin (H&E) staining)

(Fig. 16.7) (KOSSA staining), as well as atherosclerotic plaque with calcium in the intima. Calcium powder in the area of the internal elastic lamina can be seen in the same female patient (Fig. 16.8).

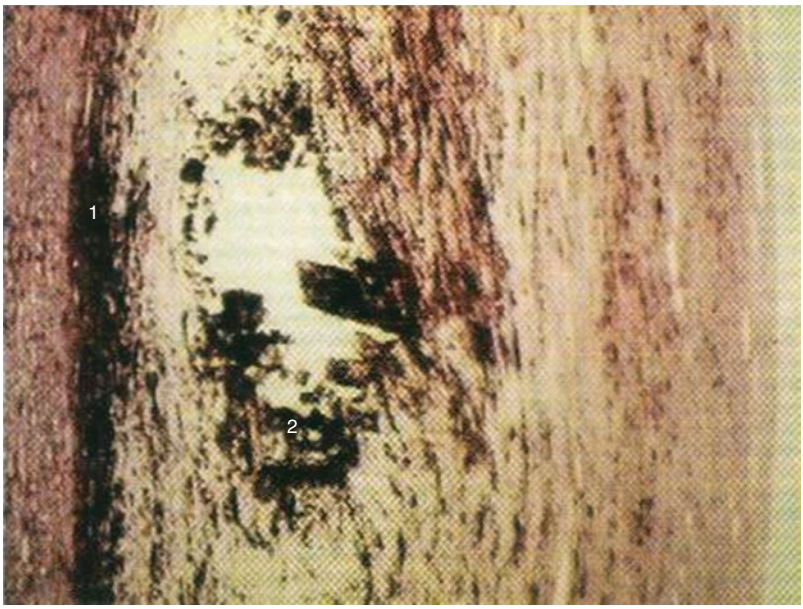

Fig. 16.7 Deposits of calcium (*1*) in the area of the internal elastic lamina and sclerotic plaque with calcium in the intima (*2*) (KOSSA+HE staining)

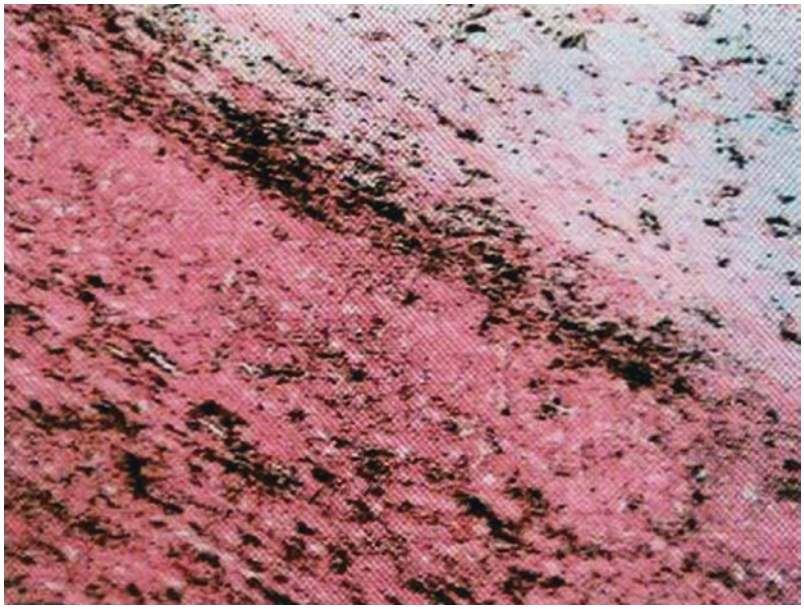

Fig. 16.8 Typical image of calcium powder in the internal elastic lamina (KOSSA+HE staining)

Calcifications in the internal elastic lamina are one of the typical GCA features. Giant cells obviously attack the internal elastic lamina and incorporate the calcified parts of the membrane. It seems that calcifications in the region of the internal elastic lamina and atrophy of the media are inevitable prerequisites for an inflammatory reaction [23].

Calcifications of the internal elastic membrane morphologically differ from those seen in the Mönckeberg medial calcific sclerosis, as well as from atherosclerotic calcifications in the intima [24], as shown also in our Fig. 16.7. This difference in morphology is probably the cause of concentration of giant cells around calcium in the internal elastic lamina. Analysis of blood vessel segments not affected by the inflammatory response showed a significantly greater atrophy of the smooth muscles of the media and calcifications in the area of the inner elastic membrane, as compared with the group of healthy individuals. The involvement of arteries at the beginning of the disease may be caused by metabolic disorders in the arterial wall. This gradually leads to atrophy of the smooth muscles of the media and to degeneration and dystrophic calcifications of the inner elastic membrane.

Giant cells developing around foreign corpuscles come probably from smooth muscles and then they respond to the presence of a degenerated and calcified internal elastic membrane. Giant cells serve as antigens for lymphocytes that subsequently produce cytokines. Due to them macrophages flow to the affected site and cause severe damage to the vessel wall by inducing oxidative reaction in the media affecting its smooth muscle cells, as well as by producing reactive oxygen and nitrogen intermediates which together with metalloproteinases fragment elastic membranes. Increased permeability of the fragmented internal elastic lamina allows for entry of migratory fibroblasts that later cause its hyperplasia and occlusion of the blood vessel lumen [25].

Development of a hyperplastic intima is accompanied by intensive neoangiogenesis. While in normal arteries the presence of vasa vasorum is restricted to the adventitia, in the case of inflamed arteries, the capillaries grow into the media and the intima [26]. Neovascularization was observed also in our group of patients, as shown by the histological image of the aorta of an 86-year-old man (Fig. 16.9) and its detail in Figs. 16.10 and 16.11. Figure 16.11 shows a detail of the neovascularization site in the aortic media with inflammatory infiltration and destruction of elastic fibers of the media.

Inflammation of blood vessels in GCA is of segmental nature. Intensity of inflammatory response varies in individual parts of the same blood vessel or between individual blood vessels and changes in different stages of the disease. Typical features of granulomatous inflammation are observed in about 50% of patients, the other half of patients with a positive histological finding exhibit panarteritis with a mixed inflammatory infiltrate, which is primarily of lymphomononuclear nature, with a few neutrophils and eosinophils, but without giant cells. Such panarteritis, consisting of a mixed inflammatory infiltrate composed of polymorphonuclear leukocytes, lymphocytes, and plasma cells, can be seen in Fig. 16.12 of the aorta of our female patient (hematoxylin and eosin (H&E) staining).

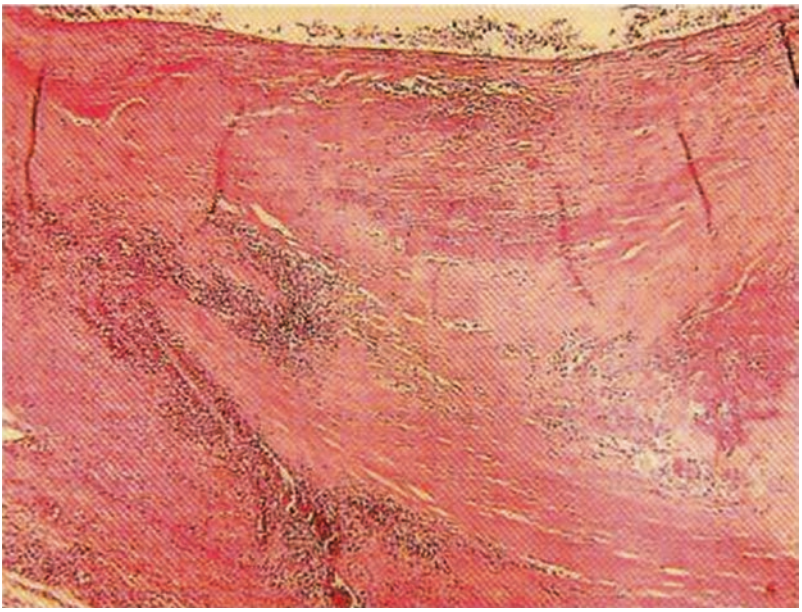

Fig. 16.9 Neovascularization in the aortic media of an 86-year-old man with GCA

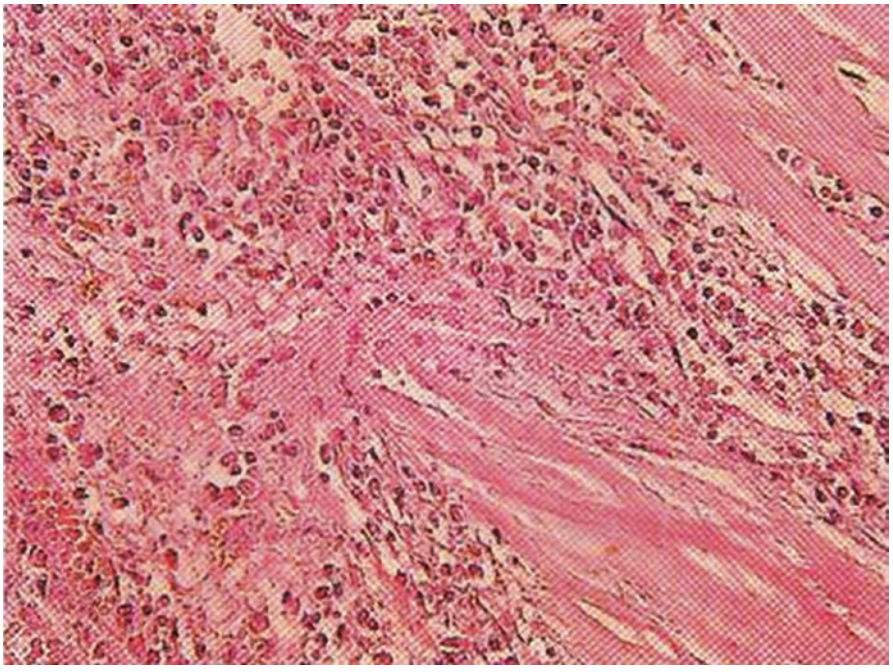

Fig. 16.10 Detail of neovascularization in the aortic media with inflammatory infiltration and destruction of elastic fibers

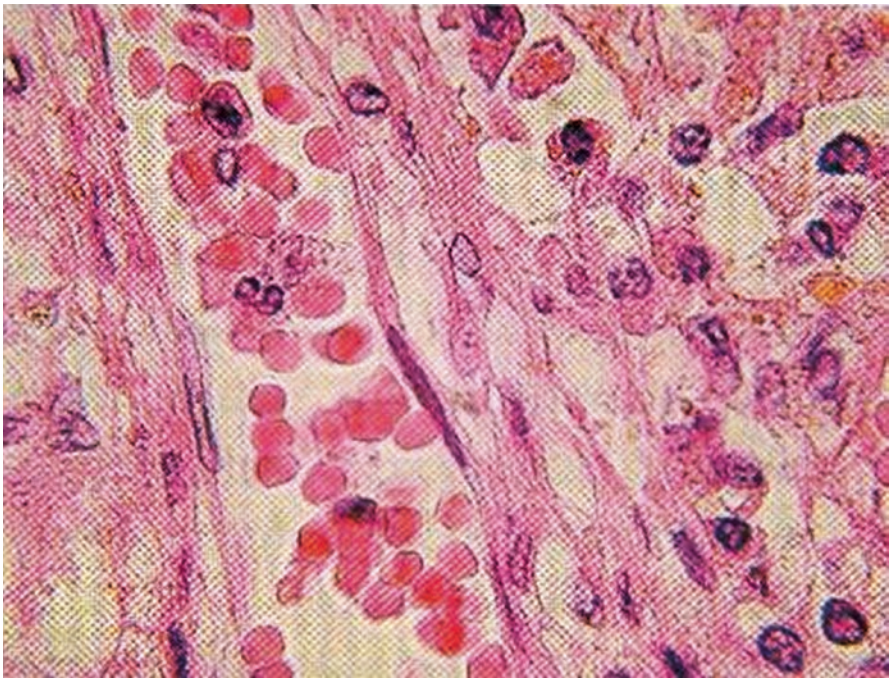

Fig. 16.11 Neovascularization—greater detail than in Fig. 17.14

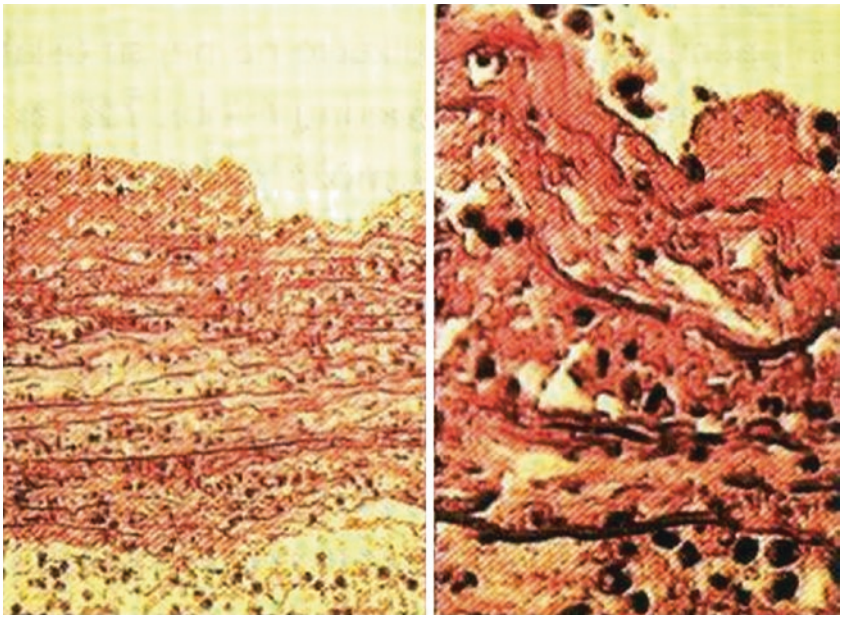

Fig. 16.12 Panarteritis with a mixed inflammatory infiltrate (hematoxylin and eosin (H&E) staining)

16.4 Clinical Features

GCA onset and course are highly individual. Patients may complain of headache or rheumatic pain of joints and muscles, typical of polymyalgia rheumatica (Table 16.1). The most common clinical features include headache and painful swelling above the temporal artery in the elderly individuals (Fig. 16.13). A typical clinical manifestation of GCA is a sharp, throbbing headache, located mainly in the temporal, less frequently in the occipital area, sometimes radiating to the neck, cheek, jaw, or tongue. It occurs in about two thirds of patients as a new or altered headache, unresponsive to common analgesics. Patients often complain of palpation tenderness in the temporal area, which they feel especially during hair combing. The affected temporal artery is usually thickened and tender, with reduced pulsation, and the patient has red patches on the scalp, including localized hair loss (Figs. 16.14 and 16.15) [27].

As the disease may involve any medium- or large-sized artery, not only the temporal artery, the range of clinical features may be much wider. In addition to headache, they include nausea, fatigue, fever, masseter claudication and pain in

Table 16.1 Clinical features of the giant cell "temporal" arteritis

1.	Headache
2.	Painful induration and red patches above the temporal artery
3.	Claudication pain in jaw muscles and/or tongue
4.	Chronic throat pain
5.	Ocular symptoms with subsequent blindness
6.	Polymyalgia rheumatica
7.	Raynaud's phenomenon, paresthesia, and claudication in extremities
8.	Dissecting aneurysm of aorta, rupture of aorta
9.	Signs of myocardial ischemia
10.	Signs of cerebral ischemia

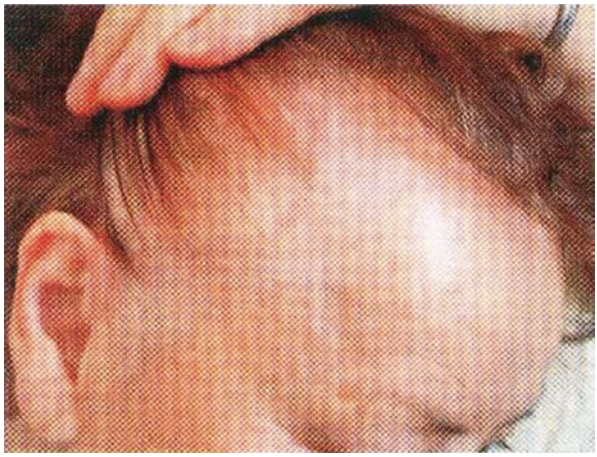

Fig. 16.13 Enlarged temporal artery in a female patient with GCA

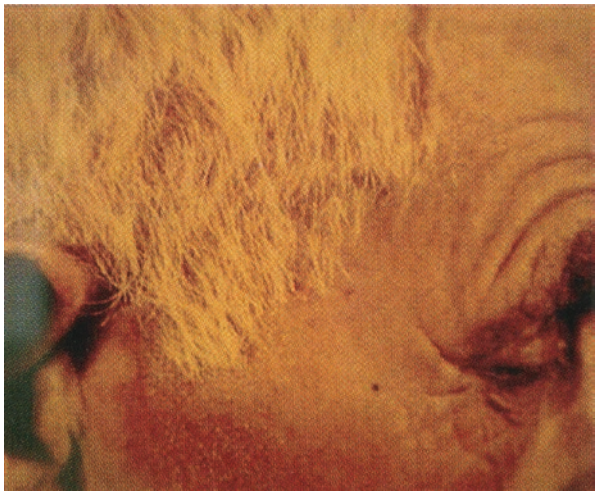

Fig. 16.14 A patient with histologically proven temporal arteritis

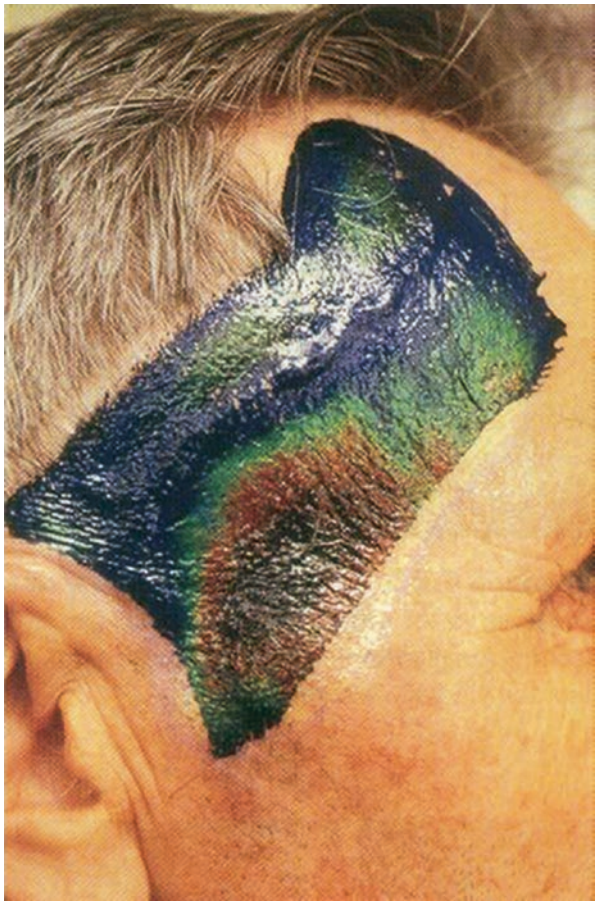

Fig. 16.15 Thermographic image of the temporal arteritis site showing increased temperature gradient in the area of superficial temporal artery

the tongue, chronic throat pain and painful nodules, or induration of the skin on the scalp. The onset of the first symptoms is usually sudden, even dramatic. Some patients exhibit only general symptoms such as loss of weight, fever, weakness and loss of appetite. Establishment of diagnosis in these patients is highly difficult.

One of the most frequent and the most severe manifestations of GCA is visual disturbance. Visual symptoms occur independently of a systemic damage in 5–38% of patients. Patients complain of decreased visual acuity and pain around the eye. Temporary or permanent loss of vision in elderly patients must be examined in terms of suspected GCA (Fig. 16.16). The most common diagnosis is anterior ischemic optic neuropathy manifesting itself by a sudden unilateral or bilateral loss of vision that may be pain free (78–99%) [28].

The classical finding is a pale swelling of the optic nerve disc which gradually changes into atrophic disc with excavation. A different finding is nonarteritic neuropathy of the optic nerve, with hyperemic oedema of the optic nerve disc gradually progressing to segmental atrophy without excavation [29], that may be associated with a central or segmental occlusion of the retinal artery [30]. Another symptom may be diplopia resulting from ischemia of oculomotor muscles or nerve (Fig. 16.17). The oculomotor nerve is affected most often; however, pupillary reaction remains intact. The most feared complication in GCA is loss of vision that may have an abrupt onset, be initially confined to one eye, and attack the other eye after a short interval [6]. Loss of vision may result either from ischemic neuritis of the optic nerve or from occlusion of the central retinal artery.

Polymyalgia rheumatica is a condition so closely associated with temporal arteritis that some authors consider it as a part of the same common syndrome [31]. It occurs in about half of patients with GCA, and, vice versa, about 50% of patients with symptoms of polymyalgia have a positive temporal biopsy finding. The main

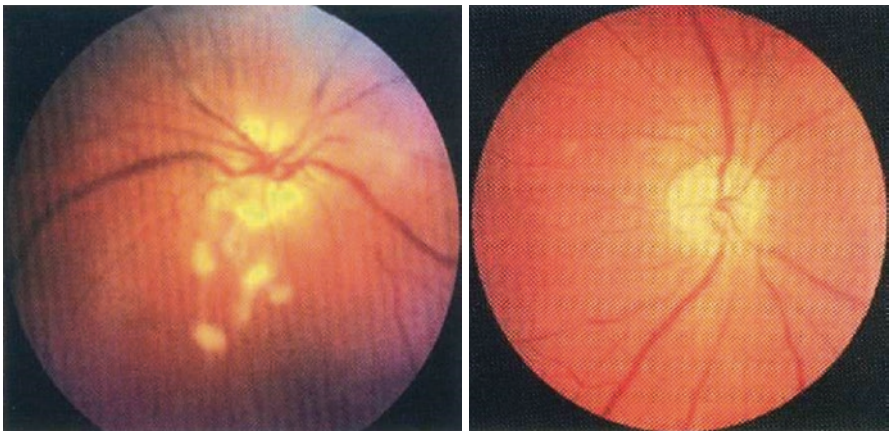

Fig. 16.16 GCA complications in our group of patients. *Left*—ischemic changes of optic nerve disc and retina of the right eye prior to corticosteroid treatment; *right*—fundus after corticotherapy. Treatment with high glucocorticoid doses saved the patients' sight

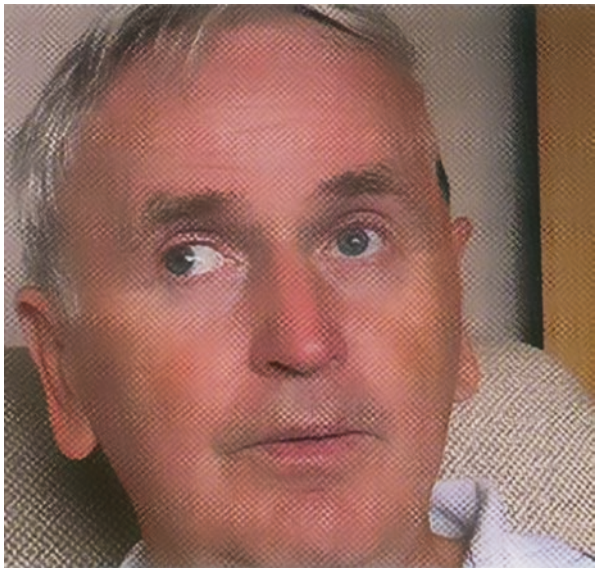

Fig. 16.17 GCA associated with oculomotor nerve palsy (convergence insufficiency)

clinical findings include pain and stiffness of at least two of the following regions: shoulder girdle, pelvic girdle, and neck muscles, persisting for more than a month. The pain is usually symmetrical, occurring during physical inactivity and at night, accompanied by morning stiffness, which often dominates [10]. Muscles are tender to palpation, without swelling. Patients have problems getting out of bed or up from a chair or combing their hair without assistance. Later, the pain becomes permanent. Physical examination reveals limited shoulder elevation and pain in intra-rotation, limited hip rotational motion, and trapezius pain during neck movements. If untreated for a long time, the disease leads to gradual muscle atrophy. Patients relatively often complain of arthralgia. The findings of joint involvement are mostly insignificant. A total of 10–60% of patients may have oligoarticular synovitis of peripheral joints in the initial stage of the disease [32]. It affects most frequently the wrists, knees, and metacarpophalangeal joints. Synovitis of joints is usually episodic and quickly subsides when treated by low doses of glucocorticoids [33].

Involvement of the aorta and its branches is observed in about 10–15% of GCA patients. The symptoms indicating involvement of large arteries include Raynaud's phenomenon, paresthesia, and claudication in extremities. Involvement of the aorta can be life-threatening due to the development of a dissecting aneurysm or rupture of the aorta [3]. Macroscopic image of the aortic arch shows a split aortic wall with blood clots (Fig. 16.18). Figure 16.19 presents dissection in the media, where blue color represents fibrin, which is a proof of blood flowing in the false lumen of the dissecting aneurysm (phosphotungstic hematoxylin staining) [7]. In patients with GCA, the probability of development of aneurysm of the thoracic aorta is 17.3 times higher and that of the abdominal aorta 2.4 times higher as compared to the healthy population [34]. Although lesions of coronary arteries are not very frequent in GCA, acute myocardial infarction was also several times reported in the literature as the

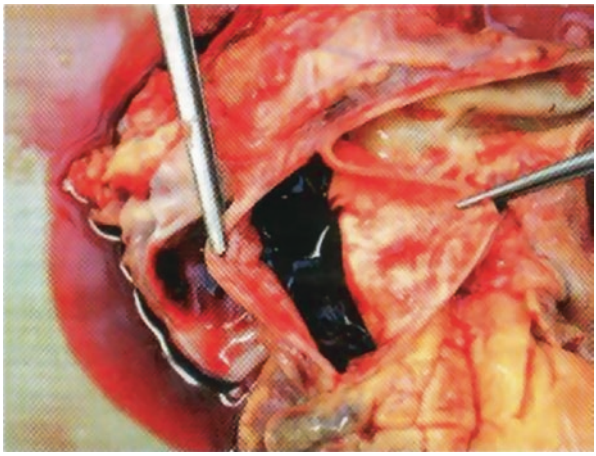

Fig. 16.18 Macroscopic image of the aortic arch showing a split aortic wall with blood clots

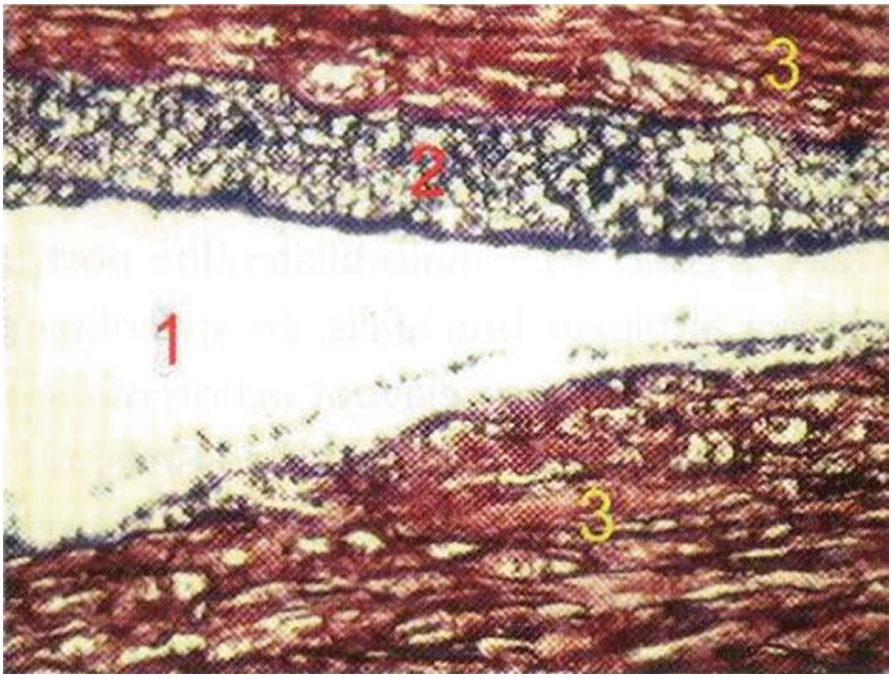

Fig. 16.19 Dissecting aneurysm of the aorta—dissection (*1*), fibrin (*2*), media (*3*) (phosphotungstic hematoxylin staining)

cause of death [6, 35–37]. Involvement of the carotid and vertebrobasilar arterial systems may result in stroke [2], but also other neurological symptoms were described, such as confusion, dementia, depression, tinnitus, hearing disorders, mononeuritis multiplex, peripheral neuropathy, and cranial nerve disorders, e.g., oculomotor nerve palsy [38].

Neurological symptoms occur in about 20–30% of patients. They most probably result from vasculitis of nutritive blood vessels or from spreading of inflammation from arterial walls to the surrounding tissues. Clinical manifestations may comprise hearing loss, hemiparesis, depressions, confusion, and in 10–15% of patients peripheral neuropathy. Neuropathies are often diagnosed before GCA diagnosis is established. A review published in the English literature reports 50 cases of neuropathy caused by GCA, of which in 40% the involvement was bilateral, affecting most frequently the median nerve. The brachial plexus may also be involved which makes it difficult to distinguish the disease from oppression of the C5–C6 root. A frequent presenting feature of the disease is involvement of facial muscles in the form of masseter claudication while chewing solid food, pain in the tongue, rarely microstomia, or trismus [39–41]. Cerebrovascular disorders, such as strokes or transient ischemic attacks (TIA), are according to Nesher [39] quite rare in GCA. In a cohort of 166 patients with biopsy-proven GCA, TIA occurred in 6% and stroke in 3% of patients. GCA shows a higher incidence of ischemia of vertebrobasilar blood vessels (40–60%) as compared to atherosclerosis (15–20%) [42]. Neuropsychiatric manifestations of GCA include disorientation, dementia, impairment of cognitive and memory functions, mood changes (depression), and psychoses. Visual hallucinations have been reported in patients with a vision impairment or loss. It should be noted that GCA is one of the manageable causes of dementia and glucocorticoid therapy in these patients may stabilize its symptoms and improve the patient's condition. As the hormone therapy alone aggravates initially psychotic manifestations, it has to be combined with antipsychotic drugs [42]. Audiovestibular manifestations were detected in about 7% of patients, most often in the form of unilateral or bilateral hearing loss, vertigo, and tinnitus.

One of the quite rare GCA manifestations is involvement of the arteries of the upper and lower extremities. The most severe symptom of a vascular disease of extremities is an abrupt onset of bilateral and rapidly progressing claudication with reduced or even absent peripheral pulsation. In the upper extremities, the subclavian and the brachial arteries and their branches are usually affected (Fig. 16.20), while

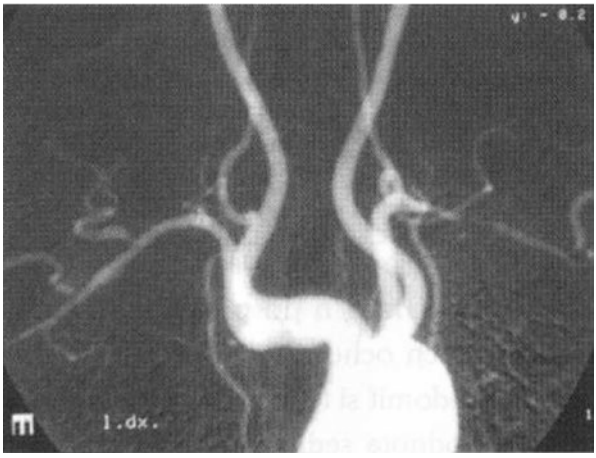

Fig. 16.20 Angiography of an 81-year-old female patient with GCA—stenotizing changes in arteries of both upper extremities

in the lower extremities the femoral superficial and popliteal arteries are commonly involved. Clinical features include claudication, sometimes critical limb ischemia. Claudication is in most cases bilateral. Patients are at risk of a sudden occlusion of the blood vessel with ischemia and subsequent gangrene in the respective region (Fig. 16.21). Only a few patients with limb ischemia and histologically proven GCA have been reported in the literature up to now. The initial symptom of ischemia in extremities is usually claudication pain. Garcia Vázques et al. [43] report a

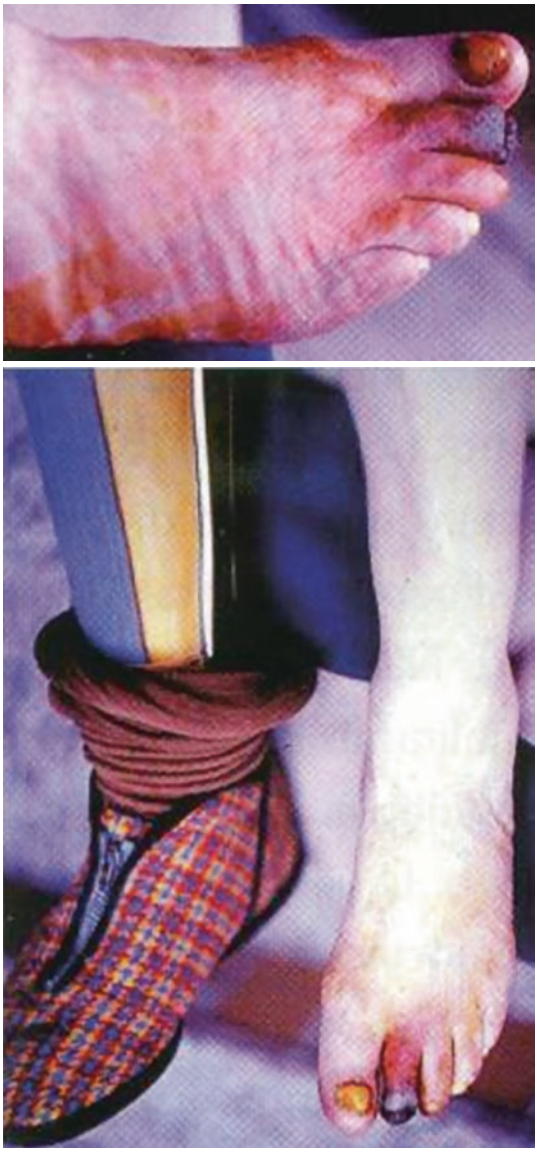

Fig. 16.21 GCA complications in our group of patients. Fatal consequences of PMR/GCA in histologically proven arteritis of peripheral blood vessels of lower extremities with a subsequent gangrene and amputation of the right lower leg and the condition of the left foot. After the last complication, the patient's condition was complicated by embolization into the pulmonary artery

52-year-old woman with ischemia of upper and lower extremities, suffering from ischemic pain for 6 months. Bruits could be heard along the course of both femoral arteries. No risk factors typical of atherosclerosis, such as smoking, hypertension, hypercholesterolemia and elevated triglyceride levels, or diabetes mellitus, were identified in the patient. Ischemia in the left lower extremity was gradually getting worse, reaching degree III according to the Fontaine's score, including bilateral loss of lower limb pulsation. Temporal arteries were palpable but not painful. The patient had a high sedimentation rate and increased serum albumin values. Angiography revealed narrowing of both subclavian arteries, segmental stenoses and filiform stenosis of the left superficial femoral artery, and multiple lesions and stenoses of the whole right artery. The bioptic material taken from the temporal and femoral arteries contained multiple giant cells, confirming GCA diagnosis.

Bilateral sympathectomy was performed with poor results, while glucocorticoid treatment with 40 mg daily dose was efficient. Another angiographic examination performed after 2 years showed a marked improvement of lesions in both subclavian arteries and in the right superficial femoral artery. Although many segmental narrowings were found on the left side, there developed large collateral connections improving blood supply of the distal extremity.

In 1997, Dupuy et al. [44] reported two patients with GCA involving lower extremity blood vessels, where the initial manifestation of the disease was claudication pain. Claire Le Hello et al. [45] published a study of eight patients with GCA (six women and two men). They all had leg claudication with abrupt onset. Tato and Hoffmann [46] presented four cases of involvement of lower limb arteries.

GCA may be rarely manifested also by pulmonary involvement (pleural effusion, intra-alveolar bleeding) [47, 48]. Liver involvement, usually not severe, is found in about 20% of patients with GCA. It is characterized by elevation of liver enzymes. The symptoms resolve with administration of corticosteroids. The bioptic finding is commonly normal, although there may occur a portal or intralobular inflammatory infiltration and rarely also granulomatous inflammation [49]. Renal involvement is infrequent and includes microscopic hematuria, mild proteinuria, and only exceptionally nephrotic syndrome or impairment of renal functions [50].

Survival of patients is not significantly reduced by giant cell arteritis, provided that the treatment is timely and adequate.

Säve-Söderbergh et al. [37] describes the following causes of death in nine GCA patients: two patients died of myocardial infarction, another two of dissecting aneurysm of the aorta, and five of stroke. None of the described patients was treated with adequate corticoid therapy.

16.5 Diagnosis

Laboratory findings of both PMR and GCA are in general typical, predominated by a high, often three-digit erythrocyte sedimentation rate (ESR), as a rule more than 50 mm/h with the use of Westergren method. However, literature sources report also

cases of both diseases with lower or normal ESR values [51–53]. In cases where other symptoms are indicative of GCA, treatment of the patient should never be delayed due to normal ESR values. A significant GCA inflammation marker is C-reactive protein (CRP). Unlike ESR, it is usually not influenced by age, gender, or hematologic abnormalities. CRP values increase during 4–6 h and respond more promptly to the treatment than ESR. Both these parameters are examined routinely. Most patients exhibit a mild normochromic or hypochromic normocytic anemia [54]. Thrombocytosis occurs in about 60% of patients, while the number of leukocytes usually remains unchanged [55]. The values of alpha-2 globulins, less often of alpha-1 globulins, gamma-globulins, and fibrinogen, are increased. Muscle enzymes are within the reference range. Examination of liver enzymes reveals a mild increase especially of alkaline phosphatase [49, 56]. Interleukin 6 (IL-6) is a pro-inflammatory cytokine. It has been demonstrated that its elevated levels better correlate with the disease activity than ESR. Elevated IL-6 levels may persist also during glucocorticoid treatment as a subclinical manifestation of a clinically silent inflammation [57, 58]. Von Willebrand factor is a high-molecular-weight glycoprotein which is involved in the process of hemocoagulation. It is produced by thrombocytes and endothelial cells. Although increased values of this factor were detected in patients with PMR and GCA, its use as a marker of the disease activity has not proved efficient in practice, yet [59]. Some patients may exhibit also a low-titer rheumatoid factor [60], but anti-citrulline antibodies were not found in any of the patients with PMR [61]. The presence of this marker may help in differential diagnosis of PMR and rheumatoid arthritis developed in advanced age.

In 1990, the American College of Rheumatology (ACR) developed classification criteria for GCA diagnosis (Table 16.2), based on comparison of 214 patients diagnosed with GCA with a group of 593 patients with other forms of vasculitis [62]. A patient is said to have GCA if at least three of five criteria are present. The presence of any three or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%. Assessment of the given diagnostic criteria is relatively simple as it requires in addition to biopsy only clinical examination. The basic clinical symptoms indicative of GCA include a swollen and painful temporal artery tender to palpation, jaw claudication, loss of vision, and polymyalgia rheumatica associated with a high erythrocyte sedimentation rate. Biopsy is the only invasive procedure; it is performed under local anesthesia and is associated with minimum complications.

Since involvement of large arteries in GCA may have fatal consequences, examination of all patients should be targeted at changes in these arteries. Blood pressure

Table 16.2 Classification criteria for GCA diagnosis OBA (developed by ACR—American College of Rheumatology)

• Age at disease onset ≥50 years
• New onset of or new type of localized pain in the head
• Temporal artery tenderness or decreased temporal artery pulse
• Elevated ESR exceeding 50 mm/h
• Positive histological finding in biopsy

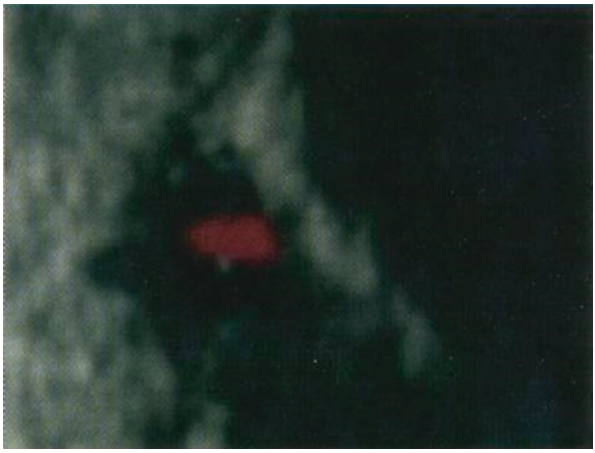

Fig. 16.22 Color Doppler ultrasonography finding and swelling of temporal artery with reduced flow rate (*red coding*) in a female patient with temporal arteritis (*cross section*)

should be measured in both upper extremities. The methods used to assess the scope of involvement of the arterial system include ultrasonography and angiography examinations. While classical angiography (DSA—digital subtraction angiography) shows primarily changes in the arterial lumen, changes in large artery walls can be well imaged by CT, MRI, and PET (positron emission tomography) [46]. A typical GCA ultrasonography finding is primarily a hypoechoic halo sign around the narrowed lumen. Ultrasonography findings of GCA in the superficial temporal artery include a hypoechoic halo sign documenting both wall swelling of the affected blood vessel and changes in the blood-flow velocity in this vessel (Fig. 16.22).

Ophthalmological examination includes mainly fluorescein angiography which reveals hyperfluorescence of the optic nerve in later stages. Occlusion of retinal arteries is confirmed by absent or retarded fluorescein perfusion during angiography. Fluorescein angiography documents that GCA affects not only large- but also medium-sized arteries (e.g., retinal and ciliary arteries) or even small arteries (small branches of retinal and ciliary arteries), the damage of which may result in loss of vision [63]. Optical coherence tomography demonstrates in vascular occlusions abnormality of the optic nerve and a later retinal atrophy. Examination of the visual field is used to monitor the progress of damage to the optic nerve.

Final diagnosis is established on the basis of a characteristic finding of panarteritis obtained during biopsy of the temporal artery or another artery affected by the disease and negative muscle biopsy. Typical GCA-related histopathological changes include granulomatous inflammation; presence of giant cells, predominantly in the media; smooth muscle atrophy and destruction of elastic fibers; splitting and fragmentation of the internal elastic lamina; as well as deposits of calcium salts in the area of the internal elastic lamina, diffuse inflammation of the vessel wall, and ingrowth of capillaries (neovascularization). As the involvement of blood vessels is segmental, and biopsy may miss the affected location, it is recommended to

examine several sections of 5–8 cm (minimum 2–3 cm) portion of the temporal artery [64]. Biopsy is important in terms of both confirmation of the diagnosis and assessment of the disease activity. It should be performed prior to commencement of therapy, as corticosteroid treatment reduces the value of bioptic examination. Biopsy is efficient in up to 80% if performed before the therapy, in up to 60% if made during the first week of the therapy, but only in 20% of patients when performed one week after full corticosteroid treatment [30].

PMR diagnosis is based on a careful assessment of clinical and laboratory parameters of the disease and primarily on exclusion of other diseases that may manifest themselves by polymyalgia syndrome. These include especially infections, malignancies, multiple myeloma, hypothyreosis, rheumatoid arthritis, or other systemic connective tissue diseases [65]. Several criteria have been set for PMR diagnosing. Criteria according to Bird et al. [66] include seven parameters:

1. Bilateral shoulder pain and/or stiffness
2. Onset of illness of less than 2 weeks' duration
3. ESR higher than 40 mm/h
4. Duration of morning stiffness exceeding 1 h
5. Age 65 years or more
6. Weight loss
7. Bilateral tenderness in the upper arm

PMR diagnosis is probable if at least three of these criteria are met or if at least one criterion coexists with a clinical or pathological abnormality of the temporal artery.

Jones and Hazleman [67] require all the criteria listed below to be met for PMR diagnosis:

1. Shoulder or pelvic girdle pain
2. Morning stiffness
3. Duration of symptoms exceeding 2 months
4. ESR higher than 30 mm/h and/or CRP more than 6 mg/L
5. Absence of rheumatoid arthritis, infectious arthritis, and malignancy
6. Absence of objective manifestations of another muscle disease
7. A rapid and significant response to glucocorticoid treatment

GCA diagnosis should be considered in all patients older than 50 years with a new onset of headache, visual disorders, myalgia, elevated ESR, and fever of unknown origin. It has to be taken into account that loss of vision sometimes occurs as early as during manifestation of the first complaints, often without prodromal symptoms. Examination should be focused on palpation tenderness along the course of arteries of the head, neck, and extremities, their swelling or change in color, detection of murmurs, symmetrical checking of peripheral pulsation in both upper and lower extremities, and measuring of blood pressure in both upper extremities. Diagnosis is established on the basis of the mentioned combination of clinical, laboratory, and bioptic tests. In case of affected large- and medium-sized arteries, a

potential involvement of atherosclerosis should be considered. It is important to take into account that arteries may be simultaneously affected by vasculitis and atherosclerotic process [68].

Differential diagnosis must be used to exclude other causes of headache that are quite frequent in this age group, such as ischemic manifestations of the CNS, inadequately compensated hypertension, intracranial tumors, or metastases of other tumors. Headache may be associated with migraine but also with the use of certain medications. The drugs that cause headache in elderly patients include mainly nitrates, hypotensive drugs (reserpine, atenolol, nifedipine), digoxin, benzodiazepines, barbiturates, nonsteroidal antiphlogistic drugs (indomethacin), H2 receptor blockers, aminophylline, theophylline, trimethoprim-sulfamethoxazole, and other drugs. In case of pain located in the jaw, it is necessary to exclude stenocardia, gastroesophageal reflux, tooth disorders, otitis, neuralgia, and osteoarthritis of the temporomandibular joint [65, 69].

16.6 Therapy

Polymyalgia rheumatica and giant cell arteritis are diseases that respond exceptionally well to glucocorticoid treatment. A prompt response to low doses of glucocorticoids is part of some PMR diagnostic or diagnosis supporting criteria [66, 67]. A common daily dose of glucocorticoids in PMR usually does not exceed 15 mg, and an even lower initial dose was reported in the literature. Based on the experience, the most suitable initial dose is 15 mg of prednisone a day. Alternate day therapy is less efficient than a single daily dose. Marked improvement can be observed as early as during 48–72 h of the commencement of glucocorticoid treatment. After resolution of clinical symptoms and decrease of inflammatory reactants, the prednisone dose is gradually decreased. In practice, the dose of prednisone is reduced most often by 2.5 mg every 4 weeks. Maintenance doses should range between 5 and 7.5 mg of prednisone daily and should be administered for at least 12 months. In part of the patients, such treatment is required for the period of 2 years and in some of them for up to 4–5 years. Nonsteroidal antiphlogistic drugs are added to glucocorticoids in order to control musculoskeletal symptoms, mainly during the period of reducing the prednisone dosage. In case of failure of therapeutic response after a two-week treatment with prednisone at the dose of 15 mg/day, it is necessary to reconsider the PMR diagnosis [70, 71].

Until recently, efficiency of the treatment was assessed only according to the present clinical symptoms and ESR values. In 2004, a set of clinical and laboratory parameters was published that were recommended for monitoring of PMR therapeutic response: CRP, visual analogue scale of pain evaluated by the patient (VASp), overall evaluation of the disease activity by the physician (VASph), duration of morning stiffness in minutes (MST), and elevation of upper limbs (EUL). The PMR activity score (PMR-AS) is calculated using the following formula: CRP (mg/dl) + VASp (0 − 10) + VASph (0 − 10) + [MST (min) × 0.1] + EUL (3 − 0). The value PMR-AS <7 indicates a low disease activity, PMR-SA of 7–17 a medium, and PMR-AS >17 a high PMR activity [72].

Unlike PMR treatment, GCA therapy begins with higher doses of prednisone or its equivalents. The main principle is to commence the glucocorticoid treatment in patients with suspected GCA as soon as possible, upon meeting three or more ACR criteria (Table 16.2) or in case of GCA history with exacerbation of neuro-ophthalmologic complications, including jaw claudication, amaurosis fugax, and other visual disturbances [73]. The initial dose of prednisone ranges around 40–60 mg daily. In case of a risk of severe ischemic complications (amaurosis fugax, monocular vision loss, initial manifestations of visual disturbances in the other eye), the patient receives intravenous pulse methylprednisolone therapy at the dose of 500–1000 mg daily for 3 days, which then continues in the form of oral treatment. Alleviation of subjective complaints is reported by patients within 48–72 h of commencement of treatment. During 2–4 weeks inflammatory parameters (ESR, CRP) decrease or return to normal. The initial dose is administered usually for 4 weeks and then it is gradually reduced, maximally by 10% of the total daily dosage at one- or two-week intervals [74, 75].

Patients are monitored during the treatment due to a risk of both disease relapse and of adverse effects of the therapy. At the beginning of the disease, checks must be more frequent, with the recommended intervals at week 0, 1, 4, 8, and 12 and afterward at month 3, 6, 9, and 12 during the first year [74]. Disease relapse should be considered with ESR > 40 mm Hg and the presence of at least one GCA clinical manifestations: fever (≥38 °C), PMR, headache or scalp tenderness, loss of vision, pain in the tongue/jaw or jaw claudication, claudication in extremities, thickening, palpation tenderness or swelling of the temporal or occipital arteries, angiographic changes indicating vasculitis of the aorta or its branches, and TIA or stroke [76, 77].

The risk of ischemic complications in patients with GCA is reduced by antiplatelet or anticoagulation therapy [78]. In order to reduce the cumulative dose of prednisone, also other DMARDs are added to glucocorticoid treatment, particularly methotrexate, however with a varying effect on reduction of the monitored parameters reported in individual studies [77, 79]. Several recent studies have presented promising results of anti-cytokine therapy (primarily infliximab and etanercept) used in patients with PMR and GCA, although the cohorts of patients were small [80, 81].

The drug of choice for treatment of both PMR and GCA still remains to be glucocorticoids. In order to reduce the risk of adverse effects, the patients receive simultaneously H2 receptor blockers or proton pump inhibitors, calcium and vitamin D supplementation, and where appropriate bisphosphonates, depending on the bone density values.

The British Society for Rheumatology published the following guidelines for GCA treatment [76]:

- *Initial treatment of uncomplicated GCA*: prednisolone 40 mg daily until resolution of symptoms and laboratory abnormalities
- *Initial treatment of complicated GCA* (visual disturbances, amaurosis fugax): i.v. methylprednisolone 500–1000 mg daily for 3 days

- *Monocular vision loss* (prevention of involvement of the contralateral eye): prednisolone 60 mg daily, addition of 75 mg daily, calcium and vitamin D supplementation, and where appropriate addition of proton pump blockers
- *Reduction of the dose*: the dose starts to be reduced after resolution of clinical symptoms and laboratory abnormalities; reduction of the dose must be slow due to a risk of disease relapse. It is recommended to administer a dose of 40–60 mg prednisolone for 2–4 weeks until resolution of clinical and laboratory manifestations of the disease. Subsequently, the dose is reduced by 10 mg every 2 weeks to 20 mg daily, then by 2.5 mg every 2 weeks to 10 mg and finally by 1 mg every month
- *Relapse treatment*: cephalgia—increasing of the dose of prednisone prior to its last reduction:
  - *Cephalgia + jaw claudication*: 40 mg prednisolone daily
  - *Visual disturbances*: 60 mg prednisolone or i.v. methylprednisolone

Certain cases of extracranial GCA may be treated with interventional radiology or surgical techniques, e.g., angioplasty [82]. GCA significantly increases the risk of development of aortic aneurysm which is often a late complication of the disease that causes death. Therefore it is important to check actively all patients for aneurysms and schedule their regular duplex ultrasonography and where necessary also CT or MRI examination. A consistent treatment of patients with a diagnosed GCA is of vital importance. Most patients who experienced dissection of the aorta were not adequately treated, as shown by their high sedimentation rate at the time of dissection (on average 62 mm during the first hour) [83]. Of great importance is also treatment of hypertension as high blood pressure was detected in up to 77% of patients with dissection of the aorta. Untreated or inadequately treated hypertension is among key factors conducing to dissection of the aorta.

Treatment of PMR and especially of GCA must be multidisciplinary due to their systemic nature. Early diagnosis, a timely and appropriate treatment, and lifelong follow-up of patients in view of the risk of ischemic complications may prevent both development of severe complications of the disease and adverse effects of the treatment.

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Juvenile Temporal Arteritis: Review

17

Jozef Rovenský

Lie et al. [1] published in 1975 a case of two young adults (aged 21 and 22 years) and two children (aged 7 and 8 years) who complained of an unsightly, soft, painless unilateral nodule in the temporal region, ranging from 0.5 to 1.5 cm in diameter, clinically diagnosed as lipoma, sebaceous cyst, or dermoid cyst. In each instance, the patient had no evidence of systemic disease or history of trauma, and the nodule was excised for cosmetic reasons. Histologic examination of the lesions showed non-giant cell granulomatous inflammation of the temporal arteries with intimal proliferation and microaneurysmal disruption of the media. Whether the lesions represent a juvenile form of temporal arteritis, an unusual form of localized polyarteritis nodosa, or Kimura disease (subcutaneous angiolymphoid hyperplasia with eosinophilia) remains conjectural.

Lahl [2] reported in 1975 two fatal cases of giant cell arteritis (GCA) with isolated involvement of intracranial arteries. The peculiarities as observed by the author in two 42-year-old male patients from his own material are the relatively young age of these patients; the duration of illness amounting to 6 weeks and 14 months, respectively, which is unusually short for vascular processes; and substantial cerebral circulation disturbances caused by inadequate oxygen supply. The symptomatology; the special clinical and neurological findings; the distribution patterns of the extra- and intracranial vascular involvement, including the dysfunctions as caused thereby; as well as pathogenesis, etiology, and considerations concerning the differential diagnosis are reported and compared with those to be found in the literature.

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Fiore et al. [3] described in 1986 an extremely unusual occurrence of giant cell arteritis in a young black man. A 20-year-old black man came for treatment of bilateral leg claudication that had been present for a 2-month period. His medical and angiographic evaluation led to an arterial biopsy that demonstrated giant cell arteritis. The patient was treated with corticosteroids and his condition has subsequently improved. Unusual variants of giant cell arteritis are discussed.

Lie and Michet [4] stated in 1988 that thromboangiitis obliterans (Buerger's disease) is a nonatherosclerotic, inflammatory, occlusive vascular disease occurring almost exclusively in young male smokers. It involves principally medium-sized and small arteries and veins of the lower and upper extremities and only rarely the visceral and cerebral blood vessels. Buerger's disease of the temporal arteries, unassociated with the involvement of blood vessels of either the upper or lower extremities, has not been previously reported. Three such cases, clinically mimicking the classic (giant cell) temporal arteritis of the elderly, are described. This unusual arterial lesion also bears some resemblance to subcutaneous angiolymphoid hyperplasia with eosinophilia (Kimura's disease).

Amato et al. [5] described in 1989 the very few cases of pulmonary vasculitis that cannot be classified into a single category of vasculitis. Authors report the first case of a vasculitic process in which pulmonary involvement with asthma, eosinophilic interstitial infiltrates, and small nodules were seen in association with jaw claudication and temporal arteritis with giant cells found on biopsy. Other signs of systemic involvement were also present such as peripheral neuropathy, hematuria with erythrocytic casts and proteinuria, pericardial effusion, and a dilated cardiomyopathy. The histopathologic picture was complex and unique. The early age of onset, the multisystemic involvement, and the prompt response to cyclophosphamide pointed to a diagnosis of "polyangiitis overlap syndrome," with some aspects of Churg-Strauss syndrome and also temporal arteritis. Physicians should be aware of these polymorphous and life-threatening pulmonary vasculitic syndromes, which require aggressive immunosuppressor therapy.

Genereau et al. [6] described in 1992 six young adult patients (19 to 32 years old): three men with temporally localized systemic vasculitis (thromboangiitis obliterans 2, Churg-Strauss angiitis 1) and three patients (two men, one woman) with isolated temporal arteritis. Temporal arteritis in subjects under 40 years of age consists of either a temporal localization of systemic vasculitis (thromboangiitis obliterans or Buerger's disease, Churg-Strauss angiitis, or polyarteritis nodosa) or a distinct entity, of which only 12 biopsy-proven cases have been reported to date. The latter is differentiated from temporal (giant cell) arteritis of the older patient by a higher incidence in men and the absence or rarity of general symptoms, ocular complications, and an accelerated erythrocyte sedimentation rate. Two types of temporal arteritides in young adults seem to be distinguishable: an asymptomatic form with an isolated temporal nodule and a more symptomatic one. In some cases, temporal arteritis in young adults corresponds to a unique entity "juvenile temporal arteritis," which seems to be different from Takayasu's arteritis, localized forms of polyarteritis nodosa, and Kimura's disease. Although its treatment remains difficult to define, therapy of the symptomatic form could include steroids, whereas the asymptomatic one seems to require only simple monitoring.

Favarato et al. [7] reported in 1993 a 34-year-old male patient who suffered an acute anterior wall infarction at age 32. Myocardial ischemia was demonstrated later by stress testing and thallium myocardial scintigraphy. Coronary arteriography revealed a proximal 90% obstruction of the left anterior descending artery. The patient was submitted to percutaneous transluminal coronary angioplasty. The procedure was unsuccessful as the catheter could not progress through the obstruction. On follow-up, there was less than ideal adherence to medical treatment, and the patient complained of occasional atypical non-effort-related chest pain. Two years later the patient suffered a large fatal myocardial infarction. Necropsy disclosed that the cause of myocardial infarction was severe coronary arteritis of left circumflex artery with giant cell granulomas.

Tomlinson et al. [8] described in 1994 a case of arteritis involving the superficial temporal artery in an 8-year-old boy. After a 2-week prodrome of headache in the right temporal region, a painful pulsatile 6-mm nodule developed. No history of trauma or systemic disease was noted. The differential diagnosis included vasculitis or thrombosis of a vascular malformation of the temporal artery. The lesion was surgically excised for both diagnostic and cosmetic reasons. Histologic features of the nodule were diagnostic of juvenile temporal arteritis and characterized by non-giant cell granulomatous inflammation of the temporal artery, occlusive fibrous intimal proliferation, and microaneurysmal disruption of the media. At 12-month follow-up, the patient was well; no recurrent lesions or systemic disease was noted. Although rare, this disease should be recognized as arteritis that affects the external carotid circulation and should not be confused with classic giant cell temporal arteritis. If physicians are aware of this benign inflammatory disease of the temporal artery in children and young adults, unnecessary treatment will not be administered.

Lie [9] reported in 1995 on juvenile temporal arteritis (JTA) as an uncommon non-giant cell arteritis of the superficial temporal artery occurring exclusively in older children and young adults without a history of trauma or evidence of systemic disease or localized symptoms. Of the six cases reported to date, there has been no recurrence after a simple surgical excision of the nodular artery for cosmetic reasons. Authors describe the first known case of bilateral JTA in a 21-year-old man, and differential diagnoses are discussed to distinguish JTA from the classic giant cell (temporal) arteritis of the elderly, which requires corticosteroid drug treatment.

Giordano [10] published in 1995 a study on Takayasu's disease and temporal arteritis as similar entities that predominantly affect women and on significant differences between them. Takayasu's disease is a rare disorder that affects the aorta and its main branches in young women, whereas temporal arteritis is a common disorder that affects small- to medium-sized arteries of elderly women. The pathology of Takayasu's disease extends to all three arterial layers, whereas in temporal arteritis the disease affects the media and adventitia less, with giant cells more prominent. The diagnosis of Takayasu's disease depends on clinical presentation and characteristics of angiography, whereas temporal arteritis is diagnosed by clinical findings and arterial biopsy. Steroids are only palliative in Takayasu's disease with a high incidence of recurrences, whereas steroids in temporal arteritis are

curative with good long-term results. Finally, surgery plays an important role in the care of patients with Takayasu's disease but is used infrequently in those patients diagnosed with temporal arteritis.

Thal et al. [11] published, despite the fact that giant cell arteritis (GCA) is a disease chiefly found in elderly patients, with intracranial vessels rarely involved, a case study in 2001 of a 19-year-old woman with GCA in the basilar and vertebral arteries. Two weeks after the first symptoms, she developed an aneurysmal dilatation of the right vertebral artery which ruptured leading to subarachnoid hemorrhage. Although the ruptured right vertebral artery was clipped neurosurgically, she died 2 days later. Autopsy revealed GCA with focal medial necrosis and intimal thickening of the vertebral arteries and the basilar artery. No other arteries were affected. In the involved vessels, the media exhibited C1q immunoreactivity. At the intimal site of the internal elastic lamina, there were increased levels of elastase. Other arterial diseases showing the pattern of GCA were excluded. This case demonstrates that GCA is not necessarily restricted to elderly people. Moreover, this case shows that a GCA-induced aneurysm is a very rare reason for subarachnoid hemorrhage even in young adults.

Redillas and Solomon [12] published in 2003 a study on temporal arteritis which was first described in the late nineteenth century. Despite considerable progress in understanding the disease, its rarity in the young and in those who are not of Scandinavian ethnicity remains unexplained. Microbiologic agents and immunologic mechanisms have been implicated as causative factors. Although steroids remain the drug of choice, the use of other immunologic therapies has been proposed. This paper reviews the disease's history, probable etiologies, clinical manifestations, and its diagnostic and treatment challenges.

Wu et al. [13] published in 2004 a case of giant cell arteritis in a woman who developed symptoms of dizziness, headache, and bilateral sensorineural hearing impairment and had one episode of transient left hemiparesis before the age of 30, although giant cell arteritis is rarely reported in people aged less than 50 years. Carotid angiography showed multiple segmental narrowing in cranial vessels. Subsequently, at the age of 31, she had weight loss and developed a fever. Chest radiograph revealed mediastinal widening, and chest computed tomography revealed dilated pulmonary arteries and veins. Coronary angiography and aortography showed irregular narrowing of the descending aorta and multiple stenosis, with aneurysmal dilatation involving the proximal and distal coronary, pulmonary, and mesenteric arteries. Multinucleated giant cells and predominant CD8+ T lymphocyte infiltration were noted in a left temporal artery biopsy specimen. The patient's age and the finding of dilated pulmonary veins and prominent CD8+ T lymphocytes in the biopsy specimen suggest that this case was a distinct form of systemic giant cell arteritis.

Fukunaga [14] described in 2005 a case of juvenile temporal arteritis, which is a rare vascular lesion in children and young adults, associated with Kimura's disease in a healthy 23-year-old asymptomatic man. The patient presented with a painless 2.5 cm nodule with eosinophilia and normal erythrocyte sedimentation rate. Histologically, the left superficial artery showed marked intimal thickening with moderate eosinophilic infiltrates, constriction of the vascular lumen, focal

disruptions of the internal elastic lamina and media, moderate eosinophilic infiltrates in the adventitia, and absence of giant cells. The subcutaneous tissue surrounding the artery was characterized by lymphofollicular hyperplasia, marked eosinophilic infiltrates in the intra- and extra-follicles with abscess, capillary proliferations, lymphocytic plasma cell and mast cell infiltrates, and fibrosis in the interfollicular region. Immunohistochemically, reticular, positive IgE staining was observed in the germinal centers. Clinically and histologically, the lesion was consistent with juvenile temporal arteritis associated with Kimura's disease. The findings indicate that both entities are closely related and juvenile temporal arteritis may be secondary to Kimura's disease.

Pipinos et al. [15] presented in 2006 a case of the youngest patient with a biopsy-proven giant cell temporal arteritis, even if temporal arteritis, particularly in its classic form, is exceedingly rare in individuals <50 years old. A 17-year-old male presented with a progressively expanding and pulsatile but otherwise asymptomatic mass in his forehead. The patient's medical history was significant for uveitis since the age of 3 and severe allergic rhinitis, mild asthma, and juvenile rheumatoid arthritis as a young adolescent. Admission laboratory values included a mildly elevated erythrocyte sedimentation rate and C-reactive protein level. A computed tomography evaluation demonstrated aneurysmal degeneration of the frontal branch of the right superficial temporal artery and confirmed no other cerebrovascular changes. Histologically, the aneurysmal arterial segment demonstrated subacute temporal arteritis. The arterial wall had a primarily lymphoplasmacytic infiltrate with rare giant cells and focally marked medial destruction. Additionally, severely obstructive intimal hyperplasia with chronic adventitial and periadventitial dense fibrosis was noted. The diagnosis of classic giant cell temporal arteritis was established from the biopsy result. Postoperatively, the patient was treated with prednisone for 3 months. Three years after surgery, the patient remains well and reports no recurrence of temporal artery disease.

Jafri et al. [16] published in 2006 a case of a young onset temporal arteritis presenting with gastrointestinal symptoms, despite the fact that giant cell arteritis, also known as temporal arteritis, is a vasculitis of unknown etiology that classically involves the wall of the large to medium size. The patient was a 48-year-old male who presented with a 2-week history of fever, diffuse abdominal pain, and malaise. He underwent a laparoscopic cholecystectomy after findings of elevated bilirubin and alkaline phosphatase as well as suspicion of porcelain gallbladder on ultrasound (or computed tomography scan). The patient subsequently developed painless, intermittent vision loss and unilateral headaches. A work-up included temporal artery biopsy, which showed marked lymphocytic infiltrate in the arterial wall consistent with temporal arteritis. The presentation of temporal arteritis may be atypical. This was a case of temporal arteritis at a young age presenting mainly with gastrointestinal symptoms.

Arnander et al. [17] published in 2006 a study on an ultrasound halo sign surrounding the temporal artery as a well-recognized feature associated with giant cell arteritis and presented a previously unreported case of this halo sign being present around the temporal artery due to angiolymphoid hyperplasia with eosinophilia (ALHE) in a young female patient.

Love et al. [18] reported in 2008 a case of a young boy who died of subarachnoid hemorrhage 29 months after coiling of a giant vertebrobasilar aneurysm, taking into account that intracranial aneurysms are rare in early childhood and there is little published information on their histology. Histology of the aneurysm revealed intramural inflammation with giant cells and fragmentation of the internal elastic lamina. The findings highlight the need for detailed examination in such cases, to elucidate the pathogenesis and pathology of cerebrovascular aneurysms in this age group.

Nesher et al. [19] presented in 2009 a case of temporal artery vasculitis (TAV) in an 18-year-old man, followed by a literature review regarding cases of all types of vasculitic involvement of the temporal arteries in the young, although TAV in patients younger than 50 years is extremely rare. Review of the English literature has been done on vasculitis involving the temporal arteries in young patients, based on a PubMed search. The result was that less than 40 cases of vasculitic involvement of temporal arteries in the young have been described. TAV in the young may be divided into three groups: juvenile temporal arteritis, a localized eosinophilic arteritis confined to the temporal arteries, seems unique to this age group. Fifteen patients with juvenile temporal arteritis were described. Other vasculitides, such as polyarteritis nodosa, Churg-Strauss syndrome, and thromboangiitis obliterans, may involve the temporal arteries in young patients. The literature search revealed 12 such cases. The least common group is arteritis in young patients, histologically resembling elderly type temporal arteritis, featuring five cases. In addition, other conditions such as Kimura disease and angiolymphoid hyperplasia with eosinophilia may resemble temporal arteritis in the young. Authors have concluded that TAV in the young is rare and differs from the classical temporal arteritis of older adults. There is an apparent overlap among several vasculitic conditions involving the temporal arteries in the young, and histological distinction may be difficult at times. The final diagnosis of the different conditions causing TAV in the young is based on a combination of clinical findings, relevant laboratory data, imaging studies, and histological findings.

Ito et al. [20] published in 2008 a study on hypereosinophilic syndrome (HES) as a multisystem disease with a high mortality rate. It is characterized by peripheral blood eosinophilia and eosinophilic infiltration of the skin and many other organs. The commonest cutaneous features include erythematous pruritic maculopapules and nodules, angioedema, or urticarial plaques. However, some case reports have indicated that eosinophilic cellulitis, cutaneous necrotizing eosinophilic vasculitis, Raynaud's phenomenon, and digital gangrene may also occur as cutaneous features of HES. Juvenile temporal arteritis (JTA) of unknown cause is characterized by an asymptomatic nodule in the temporal artery area in young adults. Histologically, the lesion is characterized by a significant intimal thickening with moderate eosinophilic infiltrates, constriction or occlusion of the vascular lumen, and absence of giant cells. Authors report a patient with HES presenting with eosinophilic cellulitis, Raynaud's phenomenon, digital gangrene, and JTA. JTA may also be one of the features of HES.

Dinesh et al. [21] described in 2009 temporal (giant cell) arteritis as a chronic vasculitis of large- and medium-sized vessels which usually occurs in individuals above 50 years of age. In patients less than 50 years, temporal artery vasculitis is extremely rare. The clinical presentations of the vasculitis in younger patients

appear to be different from the older patients. Authors present two case reports of temporal artery vasculitis in patients less than 50 years old, one of them with human immunodeficiency virus infection. Both cases had variable clinical presentations and good response to treatment.

Durant et al. [22] presented in 2010 a case of juvenile temporal vasculitis (JTV) in a middle-aged woman study against the background that classic giant cell arteritis affects older adults who are aged >50 years. Temporal arteritis is uncommon in young adults, but JTV is the most frequent form found in young people. Clinical presentation is usually poor, with localized temporal inflammatory changes without consistent systemic manifestations. Generally, the patients have a benign clinical course, without ophthalmic or ischemic manifestations. In these rare JTVs, excision of the involved section of temporal artery is often curative and corticosteroid therapy is not required. The study reports a case of a 44-year-old woman who complained of violent temporal headache, with a slight inflammatory syndrome. She had no vascular systemic manifestation and no cause of secondary vasculitis. Doppler ultrasonography suggested a localized inflammatory arteritis. Temporal biopsy was performed. Histologic findings were compatible with JTV (nongranulomatous panarteritis with mononuclear cells and eosinophils). All the symptoms disappeared after excision. One year later, she remains well and reports neither systemic manifestation nor recurrence. Authors have concluded that vasculitis of the temporal arteries in young people is uncommon and JTV is rare in middle-aged people. It is necessary to search for systemic or secondary vasculitis. In contrast to giant cell arteritis, steroids are not required.

Labropoulos et al. [23] stated in 2011 that non-giant cell arteritis disease of the superficial temporal artery (STA) is rare, appearing only as case reports in the literature. There were nine patients with STA pathology: STA aneurysm ($n = 1$), pseudoaneurysm ($n = 4$), thrombosis ($n = 1$), and arteriovenous malformation ($n = 3$). Four patients had ligation and excision, three had percutaneous interventions, and one had a combination of both. All patients had immediate technical success and eight of the nine total patients had follow-up. Authors present a variety of ways to approach these unusual pathologies with percutaneous and open techniques demonstrating very good early outcome.

McGeoch et al. [24] published in 2013 two exceptional cases of temporal arteritis in the form of giant cell arteritis (GCA) which is common in the elderly but is extremely rare in patients less than 50 years of age. Authors report on two male patients: one who presented at the age of 31 years with painful, nodular swellings of both temporal arteries and whose temporal artery biopsy demonstrated a non-giant cell panarteritis with mixed inflammatory cell infiltrate typical of juvenile temporal arteritis (JTA) and the other one, aged 40 years, who presented with headache and cerebral angiography consistent with an intracranial vasculitis and whose temporal artery biopsy confirmed an authentic multinucleated GCA. The first patient spontaneously improved after biopsy, and the second patient has responded well to corticosteroid therapy. These two cases exemplify well two distinct but extremely rare forms of temporal arteritis in young patients. A third subset is that associated with a systemic vasculitis. Few cases of JTA have been reported, and authors describe in this report one of the only cases of GCA with central nervous system involvement in the young.

Akalin et al. [25] concluded in 2013 that temporal arteritis in the young is clinically and histologically different from classic giant cell arteritis of the elderly population. A male patient, aged 36 years, presented with headache and a nodule in his left temporal region. Histological examination of the nodule showed that the left temporal artery was encircled by a lymphoid tissue with prominent germinal centers. The arterial wall was infiltrated with mixed inflammatory cells, the internal elastic lamina was disrupted, and there was marked intimal hyperplasia. The patient was diagnosed with juvenile temporal arteritis. Because of persistent headache after surgical excision of the lesion, the patient was treated with prednisolone. Systemic vasculitides, classic giant cell arteritis, Kimura's disease, and angiolymphoid hyperplasia with eosinophilia should be considered in the differential diagnosis of the disease.

Shah et al. [26] focused in 2015 on giant aortic aneurysm defined as aneurysm in the aorta greater than 10 cm in diameter. It is a rare finding since most patients will present with complications of dissection or rupture before the size of aneurysm reaches that magnitude. Etiological factors include atherosclerosis, Marfan's syndrome, giant cell arteritis, tuberculosis, syphilis, HIV-associated vasculitis, hereditary hemorrhagic telangiectasia, and medial agenesis. Once diagnosed, prompt surgical intervention is the treatment of choice. Although asymptomatic unruptured giant aortic aneurysm has been reported in the literature, there has not been any case of asymptomatic giant dissecting aortic aneurysm reported in the literature thus far. Authors report a case of giant dissecting ascending aortic aneurysm in an asymptomatic young male who was referred to the authors' institution for abnormal findings on physical exam.

Campochiaro et al. [27] described in 2013 juvenile temporal arteritis as a rare inflammatory disease of the temporal arteries that affects young adults. The clinical course is benign and the surgical excision of the affected artery is usually curative. Authors report a case of bilateral juvenile temporal arteritis with significant peripheral eosinophilia and elevated IgE, refractory to surgical excision and even to a short course of corticosteroids. Methotrexate, added as a steroid-sparing agent, resulted in a good disease control.

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The Current Standardized Classification Systems and Risk Factors in Polymyalgia Rheumatica

18

Zbyněk Hrnčíř and Jindra Brtková

18.1 Introduction

Polymyalgia rheumatica (PMR) is a clinical syndrome occurring in middle-aged and elderly individuals, characterized primarily by painful stiffness of the neck, shoulder and pelvic girdles. In the Caucasian population in Europe and North America, it is the most frequent inflammatory disease in persons older than 50 years, with a peak in eighth age decade; women are affected about three times more often than men. From the viewpoint of historical epidemiology, it is remarkable that PMR prevalence largely corresponds to geographical expansion of Vikings in the second half of the first millennium AD [1]. The first cogent report of PMR was published in 1888 by William Bruce, a general practitioner in Strathpeffer Spa, under the title "Senile rheumatic gout" [2]; the term PMR [3] was suggested by Barber in 1957. Most specific facts about PMR have been acquired on the basis of clinical research conducted in the recent 50 years. Efforts during this period have been focused on a reliable recognition of PMR and early detection of dangers associated with its incidence, course and treatment. In a relatively short time interval (1979–1989), four criteria sets were formulated for PMR diagnosis [4–7]. In 2005 EULAR established a working group for comparative assessment of their reliability [8]. Based on analysis of data of 213 PMR patients from eight rheumatology centres in eight different European countries, it was recommended to use the Bird [4] or Hunder [6] criteria

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because alternative criteria may have less sensitivity in diagnosis. Difficulties in differential diagnosis in PMR and technological progress, particularly in imaging of soft tissue changes, led in the period of 2006–2015 to development of more specific protocols in PMR treatment. The most important of them, namely, 2010 BSP/BHPR guidelines [9], 2012 provisional classification criteria for PMR: a EULAR/ACR collaborative initiative [10] and 2015 recommendations for the management of PMR: a EULAR/ACR collaborative initiative [11], reflect the state of the art in the field of PMR management and are the focus of the present study.

18.2 The Current EULAR/ACR 2012 Classification Criteria for Polymyalgia Rheumatica

PMR evaluation systems of the second half of twentieth century were declared as diagnostic. The 2012 provisional PMR scoring system according to EULAR/ACR [10] is a classification which corresponds to the ACR concept of classification criteria [12] as standardized definitions in diseases without a "gold standard", with relatively homogeneous cohorts, emphasis on high specificity and accent on universality. Primarily it is an approach intended for clinical studies, without a direct guideline to commence therapy, however, pointing out that in a number of diseases classification and diagnostic criteria are very similar. Provisional EULAR/ACR 2012 classification criteria were evaluated in a 6-month prospective cohort study of 125 patients with new-onset PMR and 169 non-PMR comparison subjects with conditions mimicking this syndrome. Evaluation was based on a systematic literature review within which 68 potential criteria were identified of which 7 core criteria were accepted. Involved in the evaluation were 111 rheumatologists and 53 other specialists from North America and Western Europe. As a result a scoring algorithm has been developed (Tables 18.1 and 18.2, Figs. 18.1–18.5) for PMR classification in the patients who met the following initial/preliminary conditions: age ≥50 years, bilateral shoulder pain and abnormal ESR and/or CRP. The PMR cohort with a score ≥4 was thus discriminated from the control group with PMR mimickers with 68% sensitivity and 78% specificity; the positive predictive value was 69% and the negative

Table 18.1 EULAR/ACR (2012) provisional classification criteria for PMR (adapted according to ref. [10])

Criteria for application of the scoring algorithm met	
Algorithm without US	Score (0–6)
Morning stiffness > 45 min	2
Hip pain/limited range of motion	1
Absence of RF and/or ACPA	2
Absence of pain in other joints	1
Score ≥4 = PMR categorization	

PMR polymyalgia rheumatica, *US* ultrasonography, *RF* rheumatoid factors, *ACPA* anti-citrullinated peptide antibodies

Table 18.2 EULAR/ACR (2012) provisional classification criteria for PMR (adapted according to ref. [10])

Criteria for application of the scoring algorithm met	
Algorithm with US	Score (0–8)
Descriptors of algorithm without US	0–6
US criteria	
– At least one shoulder	1
with subdeltoid bursitis	
and/or bicipital synovitis	
and/or glenohumeral synovitis	
and at least one hip with synovitis	
and/or trochanteric bursitis	
– Both shoulders with subdeltoid bursitis,	1
bicipital tenosynovitis or	
glenohumeral synovitis	
Score ≥5 = PMR categorization	

PMR polymyalgia rheumatica, *US* ultrasonography

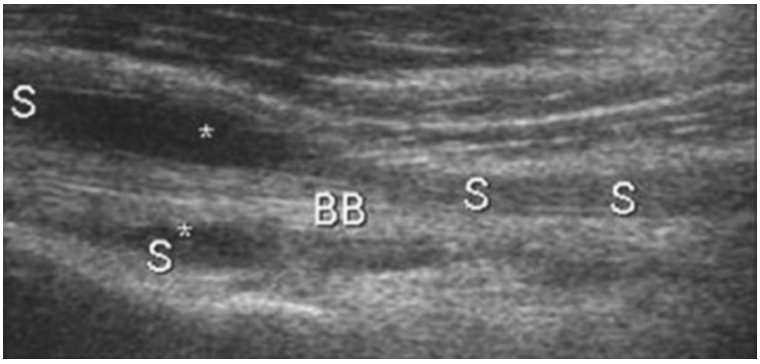

Fig. 18.1 Bicipital tenosynovitis. Bicipital groove—longitudinal view: fluid (*asterisk*) and thickened synovial sheath (*S*) in the recess of the joint capsule and around the tendon of the long head of the biceps brachii (*BB*); modified according to ref. [13]

predictive value was 77%. Ultrasound (US) changes (Figs. 18.1–18.5) alone are not specific for PMR, but they selectively increase the system specificity. The most common ultrasound (US) pathology in the given context is a biceps tenosynovitis. However, according to an observational study [14], it had no effect on the sensitivity of the EULAR/ACR 2012 criteria for PMR. Differential diagnosis in PMR is quite extensive, with the elderly-onset rheumatoid arthritis (EORA) ranking among the first in this context. A single-centre observational study [15] compared 136 patients with new-onset PMR and 149 controls, including 94 patients with RA, and demonstrated that addition of ultrasound (US) increased specificity of the scoring

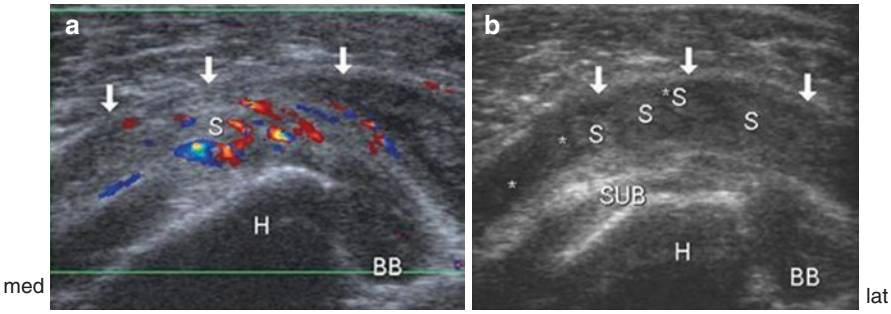

Fig. 18.2 Subacromial-subdeltoid bursitis. (**a**, **b**) (Transverse view): humeral head (*H*), tendon of the long head of the biceps brachii (*BB*), subscapularis (*SUB*), anterior recess of bursa (*down arrow*), thickened synovial sheath (*S*) and residual space of bursa filled with fluid (*asterisk*). (**a**) Hyperaemia in colour Doppler US; modified according to ref. [13]

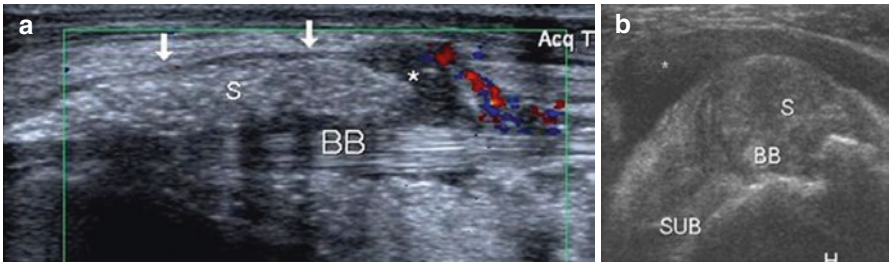

Fig. 18.3 Glenohumeral synovitis. (**a**) (Longitudinal view): recess of the joint capsule (*down arrow*), tendon of the long head of the biceps brachii (*BB*), thickened synovial sheath (*S*), fluid (*asterisk*) and joint capsule hyperaemia according to colour Doppler US. (**b**) (Transverse view): tendon of the long head of the biceps brachii (*BB*), thickened synovial sheath (*S*), subscapularis (*SUB*), fluid (*asterisk*); modified according to ref. [13]

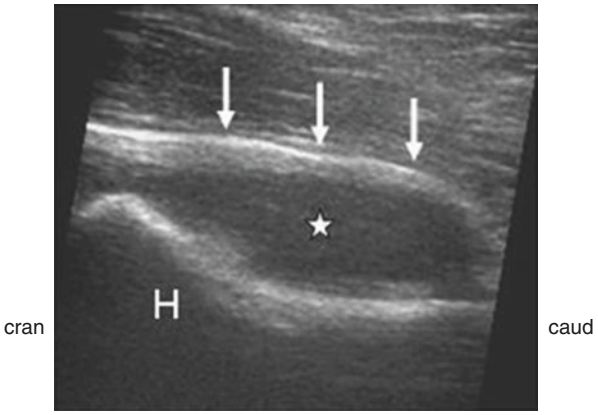

Fig. 18.4 Hip joint synovitis. Oblique parasagittal view: femoral head (*H*), joint capsule recess on the femoral neck (*down arrow*), fluid (*asterisk*); modified according to ref. [13]

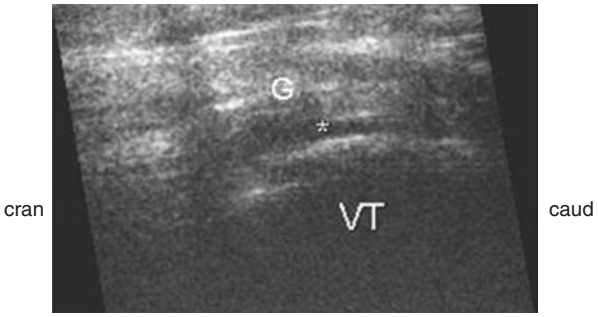

Fig. 18.5 Trochanteric bursitis. Longitudinal lateral view: greater trochanter (*VT*), gluteal muscle attachments (*G*), thin layer of fluid (*asterisk*); modified according to ref. [13]

algorithm of the EULAR/ACR 2012 classification criteria from 79.7 to 89.9% in RA. It should be noted in this context that a comparative observational study of PMR and EORA revealed anti-citrullinated peptide antibodies (ACPA) in 65% of EORA patients, whereas none of the PMR patients was positive for these antibodies [16]: however, clinical manifestations of EORA and PMR may have very similar mimickers, and seropositivity of rheumatoid factors is not a reliable discriminator. For instance, in the elderly population, the prevalence of abnormal LFT titre is increasing. This may be viewed as one of the manifestations of the changing immunological identity in the course of ageing, which complicates clinical interpretation.

The PMR concept according to the EULAR/ACR 2012 classification criteria has questioned the paradigm about a favourable therapeutic response of PMR to relatively low daily doses of glucocorticoids (GC); even a typically manifested PMR syndrome may be accompanied with insufficient GC responsiveness. Within the general evaluation of the relevance of the EULAR/ACR 2012 classification algorithm, it should be pointed out that although it is not intended for routine clinical diagnosis, its 81% reliability exceeds the 80% considered conventionally as a limit for clinical decision making.

18.3 A Risk of Giant Cell Arteritis (GCA) in Polymyalgia Rheumatica

PMR and GCA often overlap with 18–26% of patients with PMR having GCA, while 27–53% of patients with GCA having PMR at the same time [17]. Search for GCA in PMR should be focused on the facts summarized by the BSR/PHPR (British Society for Rheumatology/British Health Professionals in Rheumatology) guidelines as follows: (1) scalp pain, usually in the temporal area; (2) visual disturbance, including diplopia; (3) jaw and/or tongue claudication; (4) temporal artery abnormalities and changes in its pulsation; (5) cranial nerve palsies; and (6) limb claudication or other evidences of large-vessel involvement, including the aorta [9]. The

relation between PMR and GCA does not fall into the common differential diagnosis protocol, as manifestation of the PMR-GCA/GCA-PMR complex is often asymmetric, and therefore it is imperative to search for both components even if only one of them is clinically manifested. In PMR manifestation, it is necessary to search for GCA symptoms not only clinically but also by means of supporting methods, with a focus on screening for ischemic optic neuropathy with a risk of a sudden and irreversible loss of vision, and for occult aortitis with a risk of aortic incompetence and aneurysm, or stenosis of the renal artery with renovascular hypertension. A meta-analysis of 114 retrieved studies of which 41 met the inclusion criteria for GCA (1966–2000) revealed visual symptoms in 2083 patients, including diplopia in 708 and loss of vision in 341 patients [18]. The initial step in the screening is ophthalmological examination, including fundoscopy of the retina, with fluorescence angiography, if need be. A visual disorder may rarely occur also with a normal eye bulb finding, if the cause is cerebral ischemia in case of involvement of vertebrobasilar arteries. Interestingly, frequency of severe ischemic manifestations of GCA is lower if it is accompanied with a febrile condition [19–21].

18.4 Cancer Risk in Polymyalgia Rheumatica

Prevalence of both PMR and malignant tumours is characterized by a regional geographic and ethnic variability. A risk of cancer diagnosis in PMR has been pointed out mainly by numerous case reports. A more precise assessment of this phenomenon occurring in Europe is currently offered by two large studies based on data from the UK General Practice Research Database (GPRD) and data from the Swedish Hospital Discharge Register [22, 23]. Based on the GPRD data (1987–1999), 2877 cases of PMR without pre-existing cancer were matched with 9942 patients without PMR; those with a PMR diagnosis were significantly more likely to receive a cancer diagnosis only in the first 6 months after diagnosis with HR (95% CI): 1.69 (1.18–2.42). A total of 35,918 patients were hospitalized for PMR during the years 1965–2006 in Sweden; 3941 of them developed subsequent cancer, giving an overall SIR (standardized incidence ratio) of 1.19; for cancer diagnosed later than 1 year of follow-up, the SIR was only 1.06.

18.5 Management of Polymyalgia Rheumatica According to EULAR/ACR 2015 Recommendations

EULAR/ACR 2015 management strategy [11] is based on the EULAR/ACR 2012 classification system [10], accentuating the fact that inadequate responsiveness to the initial GC therapy was found in 29–45% of patients with PMR. Internationally codified recommendations are expected both to standardize and improve patient care. The summary lists the guidelines that should be respected prior to commencement of the therapy and the requirements for initiation and course of a complex therapy. In addition to the requirement of a safe diagnosis by elimination of a wide

range of PMR mimicking symptoms, initial steps include the standard scope of lab tests (ESR, CRP, complete blood count, standard biochemistry, rheumatoid factors, ACPA, bone profile, selectively ANA, ANCA and others) and determination of comorbidities, particularly those related to tolerance/risk rate of GCs, with emphasis on the risks of prolonged GC therapy in women. Special attention should be paid to atypical PMR manifestations (age < 60 let, systemic symptomatology, peripheral arthritis), as they are associated with a higher risk of inadequate responsiveness and toxicity during GC therapy. An essential prerequisite for a systematic adherence of patients to therapy is their adequate education at diagnosis and its reinforcement during the therapy by the treating physician as well as by other nursing staff; a feedback on the quality of education is the patient's ability to ask questions [24].

After meeting the conditions of the preparatory phase and after a safe exclusion of the PMR-GCA complex, initial treatment with prednisone is indicated, following the EULAR/ACR 2015 algorithm [11] (Fig. 18.6), namely, in a single daily dose of 12.5–25 mg, tapered in view of predictable risks, but never less than 7.5 mg or more than 30 mg daily. Within 4–8 weeks, the GC daily dose may be gradually reduced to the dose of 10 mg prednisone or its equivalent, which in case of relapse is increased to the initial dose. An alternative to oral GCs may be a therapy with intramuscular (i.m.) methylprednisolone at 3-week intervals, at the dose of 120 mg in weeks 0–9 which is then gradually reduced according to the recommended protocol [11]. In patients at a high risk for relapse or toxicity induced by prolonged therapy

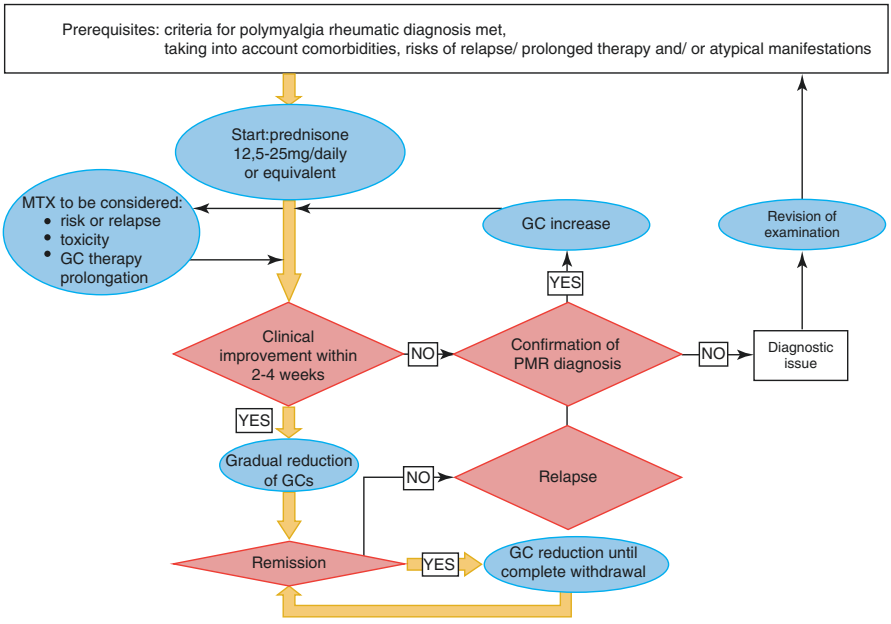

Fig. 18.6 PMR therapy algorithm according to EULAR/ACR 2015 recommendations (modified according to ref. [11])

(e.g. in patients with diabetes), early introduction of methotrexate (MTX) at the dose of 7.5–10 mg/week is recommended. Inclusion of the TNF inhibitors (TNFi) has been rejected with reference to the risks listed in the EULAR 2013 recommendation [22] on safety of disease modifying therapy in RA. No recommendation could be made for the use of non-TNFi biologic agents due to lack of adequate evidence, and the use of the Chinese herbal preparations (Yanche and Biqi) was rejected. An indispensable part of a comprehensive treatment of elderly patients are individualized exercise programs aimed at the maintenance of muscle mass and function.

In case of inadequate PMR responsiveness to a standard therapeutic protocol, it is necessary to reconsider the optimal treatment in each particular patient and his/her adherence to therapy and, last but not least, to check plausibility of the diagnosis. For instance, Hellmann [25] in *Kelley's Textbook of Rheumatology* (2013) recommends increasing of the prednisone dose to 30 mg/day and, in case of absence of the expected response within 7 days, revision of the diagnosis. PMR therapeutic protocol is contraindicated in PMR-GCA complex, which must be treated using the therapeutic protocol for GCA, as clearly indicated by BSR/BHPR 2010 guidelines [9].

Therapy beyond the recommended procedures should be considered as an individualized, actually experimental approach to inadequate responsiveness in case of repeatedly verified correct PMR diagnosis or, more often, in case of intolerance in polymorbid patients. Medicaments of choice in such situation are biologic agents from the anti-TNF-alpha group or specific for the IL-6 receptor [26–28].

18.6 Evaluation of Remission and a Risk of Relapse in Polymyalgia Rheumatica

For more than 10 years, PMR remission has been numerically expressed with the use of a disease activity score system developed by Leeb and Bird [29], based on five descriptors (Table 18.3). A composite PMR activity score (PMR-AS) is calculated as a sum of partial values, allowing comparable measurement of PMR activity over time, assessment of responsiveness as well as a risk of impending relapse.

Table 18.3 Polymyalgia rheumatica activity score (PMR-AS) according to Leeb and Bird (adapted according to ref. [28])

Descriptor	Assessment
Patient's assessment of pain	VAS 0–10
C-reactive protein	mg/dl
Physician's global assessment	VAS 0–10
Morning stiffness	minutes × 0.1
Ability to elevate upper limbs	0–3

According to the level of the shoulder girdle: 0 = above, 1 = up to, 2 = below, 3 = none; PMR-AS value = sum of values of individual descriptor

PMR-AS values <7 indicate low, 7–17 medium and >17 high disease activity. PMR-AS system has been recently reviewed on the basis of the principles of Delphi survey [30] with the conclusion that the given descriptors are relevant for continuous PMR assessment; and hip symptoms have been added to the system. In this modification, PMR-AS of 0–1.5 indicates remission and values >6.6 indicate a relapse, taking into account that the dynamics of time series measurement provides more reliable evidence than a single value. Valuable for assessment of the risk of relapse are data from longitudinal observational studies, focused on acute-phase reactants. For instance, a cohort of 94 patients with PMR was monitored for clinical signs and symptoms, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and serum interleukin-6 (IL-6) for a mean of 39 months [31]. Forty-seven (50.0%) patients had at least 1 relapse and 24 (25.5%) had at least 2 relapses during the follow-up period. A remarkable fact in this context was persistence of elevated CRP and IL-6 values also in patients with ESR within a physiological range, i.e. with a reversed intersection of the CRP and ESR curves than is usually seen in such laboratory monitoring of subsiding activity in inflammatory diseases.

18.7 A Risk of Glucocorticoid-Induced Osteoporosis in Polymyalgia Rheumatica

Long-term exposure to GCs is always associated with a risk of osteoporosis. The GC tapering schedule recommended by EULAR/ACR 2015 [11] assumes a minimum of 12 months of treatment. A more specific recommendation is currently impossible due to the lack of studies focused on this issue. The given scheme naturally does not exclude individual justified cases of 2–5-year therapy, e.g. those where involvement of MTX was impossible. Early introduction of MTX to the therapeutic protocol in addition to GCs is considered not only on the basis of the reasons mentioned in the PMR pharmacotherapy algorithm (Fig. 18.6) but also indirectly in view of evidence of the MTX osteoprotective potential in early RA, as documented, e.g. by a double-blind randomized controlled trial on prednisone at the dose of 10 mg/day [32]. Regardless of these circumstances, osteoporosis is the major risk associated with long-term GC therapy which must be combined with prophylactic administration of calcium and vitamin D: in ACR/2010 recommendations [33], it is 1200–1500 mg of calcium and 800–1000 IU of vitamin D daily [34].

Conclusion

PMR has been the subject of rational analyses for slightly more than 50 years. During this historically short period, it has been demonstrated that in the Caucasian race in Europe and North America, it is the most common inflammatory rheumatic disease in patients older than 50 years. The imperative requirement of a prompt and at the same time reliable diagnosis, early recognition of pitfalls in prognostication and optimization of a long-term pharmacotherapy, often associated with certain risks, have been recently reflected in the joint multicentric initiatives of EULAR and ACR. As a result, standardized classification

criteria for PMR have been developed that meet also requirements for clinical decision making, with recommendations for therapy as well as emphasis on individualized approach and variable options in order to achieve the set goal, i.e. a successful and safe management of the disease. The main objective of the present study was to facilitate incorporation of these facts into routine rheumatology practice.

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Giant-Cell Arteritis: Review

19

Jozef Rovenský

Guida et al. [1] published in 2014 a study on giant-cell arteritis, a systemic vasculitis characterized by granulomatous inflammation of the aorta and its main vessels. Cardiovascular risk, both for arterial and venous thromboembolism, is increased in these patients, but the role of thromboprophylaxis is still debated. It should be suspected in elderly patients suffering from sudden onset severe headaches, jaw claudication, and visual disease. Early diagnosis is necessary because prognosis depends on the timeliness of treatment: this kind of arteritis can be complicated by vision loss and cerebrovascular strokes. Corticosteroids remain the cornerstone of the pharmacological treatment of GCA. Aspirin seems to be effective in cardiovascular prevention, while the use of anticoagulant therapy is controversial. Association with other rheumatological disease, particularly with polymyalgia rheumatica, is well known, while possible association with antiphospholipid syndrome is not established. Large future trials may provide information about the optimal therapy. Other approaches with new drugs, such as TNF-alpha blockades, Il-6, and IL-1 blockade agents, need to be tested in larger trials.

Brister et al. [2] described in 2002 a case of a young woman presenting with signs and symptoms of chronic thromboembolic pulmonary hypertension who underwent pulmonary thromboendarterectomy (PTE) with concomitant coronary artery bypass. She died in the intensive care unit 1 day postoperatively. At autopsy the patient was found to have giant-cell arteritis of the pulmonary arteries and ascending aorta. It is important to differentiate this disease from chronic thromboembolic pulmonary hypertension because its management and that of systemic vasculitis differ considerably.

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Manfred Herold [3] presented in 2013 a study on vasculitis as an inflammation of the blood vessel wall causing damage to the wall followed by a wide variety of signs and symptoms, depending on the type of vessels and organs affected. Inflammation-caused vessel wall injury leads to vascular stenosis, occlusion, aneurysm, and bleeding. Thrombosis is not a common symptom but may occur, resulting in serious complications in various conditions of vasculitis.

Ness et al. [4] described in 2013 giant-cell arteritis (GCA) as the most common systemic vasculitis in persons aged 50 and above (incidence, 3.5 per 100,000 per year). It affects cranial arteries, the aorta, and arteries elsewhere in the body, e.g., in the limbs. Authors selectively review the pertinent literature, including guidelines and recommendations from Germany and abroad. The typical symptoms of new-onset GCA are bitemporal headaches, jaw claudication, scalp tenderness, visual disturbances, systemic symptoms such as fever and weight loss, and polymyalgia. The diagnostic assessment comprises laboratory testing (erythrocyte sedimentation rate, C-reactive protein), imaging studies (duplex sonography, high-resolution magnetic resonance imaging, positron emission tomography), and temporal artery biopsy. The standard treatment is with corticosteroids (adverse effects: diabetes mellitus, osteoporosis, cataract, arterial hypertension). A meta-analysis of three randomized controlled trials led to a recommendation for treatment with methotrexate to lower the recurrence rate and spare steroids. Patients for whom methotrexate is contraindicated or who cannot tolerate the drug can be treated with azathioprine instead. Giant-cell arteritis, if untreated, progresses to involve the aorta and its collateral branches, leading to various complications. Late diagnosis and treatment can have serious consequences, including irreversible loss of visual function.

Rogers and Young [5] in 2008 on a 56-year-old woman presented with a pale, painful, paresthetic right arm. Examination revealed a cold right hand, with absent right radial, ulnar, and brachial pulses. A provisional diagnosis was made of thrombotic or embolic arterial occlusion; the patient was anticoagulated and referred to the vascular surgical service. Magnetic resonance angiography showed an occluded right brachial artery. Ultrasonography confirmed this, but also demonstrated widespread narrowing of the vessel, with surrounding hypoechoic tissue and fluid within the connective tissue suggesting an inflammatory process. On questioning, the patient admitted to occipital headache and scalp tenderness. The erythrocyte sedimentation rate was 63 mm/h, and the C-reactive protein level 155.1 mg/L. A temporal artery biopsy showed changes typical of giant-cell arteritis. Prednisolone 60 mg daily was commenced with good effect. However, the patient's symptoms recurred when steroids were tapered below 50 mg daily. Moreover, 2 months later she developed bilateral calf claudication at 100 yards. Magnetic resonance angiography of the legs demonstrated narrow, diseased anterior and posterior tibial arteries bilaterally, but normal peroneal and proximal vessels. Cyclophosphamide treatment was started, with resolution of the claudication and other symptoms.

Sharma et al. [6] pointed out in 1998 that although arteritis of the gastrointestinal tract is well known, an isolated phlebitis without associated arteritis of the colon and cecum is rare. Authors describe a distinct form of giant-cell phlebitis in a 16-year-old girl causing ischemic stricture of the large intestine. She presented with

subacute intestinal obstruction and was suspected of suffering from tuberculosis. However, histopathologic examination showed giant-cell phlebitis, the arterioles and arteries being spared. Although this is an extremely rare form of nonprogressive vasculitis, it should be considered in the differential diagnosis of strictures in the large intestine, especially in the young.

O'Brien and Regan [7] set in 1998 an objective to search for evidence of actinic elastotic degeneration (actinic arteriopathy) and giant-cell arteritis (GCA) in the posterior ciliary arteries of eyes from aged white Australians. Three hundred donor eyes were given to authors by the Lions Eye Bank of New South Wales at Sydney Hospital. Of these, 146 formed the basis of this study. Portions of the posterior ciliary arteries located in relation to the optic nerve heads were processed in paraffin and were then stained by a sensitive hematoxylin and eosin stain that had been especially developed to display actinic elastotic degeneration of elastic tissue. Among 60 "aged" subjects (70–90 years), a total of 41 (approximately 68%) showed definite changes of actinic elastotic degeneration in their laminae, a condition called actinic arteriopathy. One of these subjects revealed giant cells on degenerate lamina, giving a picture regarded as early (preclinical) GCA. A young "control" group of 60 subjects 17–59 years of age revealed only one subject with a similar degree of actinic arteriopathy. Authors concluded that actinic arteriopathy of the posterior ciliary arteries was more frequent and advanced in the "aged" over 70 group as compared with changes in the "young" group <60 years of age. One aged subject without a history of eye disease showed giant cells associated with elastically degenerate internal elastic lamina. Her fortuitous lesions are regarded as indicative of how GCA is likely to begin in the damaged arteries.

Saito et al. [8] in 1994 pointed out that only sporadic reports were published and that several types of coronary arteritis can result in myocardial infarction. Recently, authors have treated a 27-year-old with acute anterior myocardial infarction. Primary directional coronary atherectomy was performed in order to recanalize the totally occluded coronary artery. The atherectomized tissue consisted of thrombi and intima infiltrated with inflammatory cells and multinucleated giant cells. Underlying diseases which can result in giant-cell arteritis were excluded. This report documents that coronary arteritis can induce acute myocardial infarction and that directional coronary atherectomy can be an effective tool in the diagnostic method for coronary arteritis.

Sato et al. [9] in 1993 published a study on giant-cell arteritis (GCA) and polymyalgia rheumatica (PMR) as common diseases in the elderly. The arteritis usually affects medium-sized vessels, but large vessel involvement can also occur leading to arm claudication, bruits, loss of pulses, and pallor of the upper extremities. The differential diagnosis of large vessel arteritis includes atherosclerosis and Takayasu's disease. Atherosclerosis, which affects patients of similar age to GCA, is usually confined to the lower limbs and can be differentiated on the basis of the clinical setting and investigations such as the ESR, arteriography, and temporal artery biopsy. Takayasu's arteritis, although histologically and arteriographically indistinguishable from GCA, is predominantly a disease of young women. A patient is described who presented with upper limb ischemia. A clinical examination revealed absence

of right radial pulses and presence of murmurs at level of the carotids. The blood pressure was unrecordable in the upper right limb. The ESR was 102 mm/h and the C-reactive protein was 11.66 mg/dL. A selective arteriography of the aortic arch and its branches revealed a right subclavian artery obstruction with good collateral circulation and a left subclavian artery stenosis. The biopsy of the left temporal artery showed a typical GCA in acute stage. Treatment with prednisolone 30 mg/day was started, and 4 weeks later, the ESR had fallen to normal. In addition this case confirms that PMR implies a systemic arteritis.

Jensen et al. [10] studied in 1990 the elastolytic capacity of live human blood monocytes in patients with giant-cell arteritis (GA) and in age-matched controls. Despite normalized acute-phase reactants during glucocorticoid (GC) therapy, the basic activity of monocytes from patients with newly diagnosed GA was elevated compared with controls (80 vs. 39 ng/h, $p \leq 0.01$). The maximum response was enhanced by stimulation with immune complexes (224 vs. 125 ng/h, $p \leq 0.01$) and with phorbol myristic acetate (324 vs. 214 ng/h, $p \leq 0.01$). No age difference was found between healthy young and old people. Cell surface-related human monocyte elastolytic activity could act as a sensitive marker of cell activation in vivo.

Teja et al. [11] reported in 1980 on a 16-year-old patient with coexistent Crohn's disease and giant-cell arteritis. The unusual features of the case include presence of giant-cell arteritis of temporal arteritis type in the bowel wall, the young age of the patient, and the previously unreported association of these two pathologic processes.

Utz et al. [12] presented in 1975 a case of a young female with renovascular hypertension in which multiple stenoses affecting both renal arteries, abdominal aorta, and left axillary artery could be demonstrated. The elevated blood pressure could be normalized by bypass operation of the renal arteries. Histopathologic findings were those of giant-cell (Takayasu) arteritis.

Maksimowicz-McKinnon et al. [13] published in 2009 a study on giant-cell arteritis (GCA) and Takayasu arteritis (TAK), considered to be distinct disorders based on their clinical features, age of onset, and ethnic distribution. However, on closer examination, these disorders appear more similar than different. The histopathology of arterial lesions in these diseases may be indistinguishable. Imaging studies have revealed large vessel inflammation in at least 60% of patients with GCA. Authors questioned whether the distinctions between these diseases might in part be an artifact due to bias in gathering historical and physical data. They postulated that signs and symptoms of GCA and polymyalgia rheumatica occur in patients with TAK but have been underreported as a result of this bias. Authors performed a retrospective review of 75 patients with TAK and 69 patients with GCA (per American College of Rheumatology criteria). Signs and symptoms attributable to disease within the year before and following diagnosis, treatment and interventional outcomes, and mortality were recorded using a standardized database. All cases were evaluated by a single physician, using identical history and physical examination forms for patients with both diseases. Patients were predominantly female (TAK 91%, GCA 82%) and white (TAK 88%, GCA 95%). New headache was a presenting symptom in 52% of TAK and in 70% of GCA patients. All TAK patients underwent vascular

imaging studies and were demonstrated to have large vessel abnormalities. However, only a subset of patients with GCA (43/69, 62%) were similarly studied. Among this group, 73% of GCA patients had at least one arterial lesion identified. In both TAK and GCA, the most common sites of involvement were the aorta (TAK 77%, GCA 65%) and subclavian (TAK 65%, GCA 37%) arteries. Compared to patients with TAK, patients with GCA had a greater prevalence of jaw claudication (GCA 33%, TAK 5%), blurred vision (GCA 29%, TAK 8%), diplopia (GCA 9%, TAK 0%), and blindness (GCA 14%, TAK 0%). Symptoms, signs, and imaging abnormalities that are characteristic of GCA or TAK are often present, albeit in differing frequencies, in both disorders. These findings lend support to the hypothesis that these diseases may not be distinct entities, but represent skewed phenotypes within the spectrum of a single disorder. Differences in frequencies of manifestations may reflect a significant bias in how data are gathered for patients with each disease, as well as the influence of vascular and immunologic senescence.

Coisy et al. [14] pointed out in 2013 that retinal artery occlusions (RAO) are severe conditions threatening vision, affecting the subsequent mortality of these patients. Authors have retrospectively reviewed the workup performed in all patients diagnosed with retinal artery occlusions evaluated in two university hospitals in France (Tours and Angers). A total of 131 patients (131 eyes) with RAO were included, with a mean age of 69.5 years and male predominance (64%). Central retinal artery occlusion (CRAO) resulted in poor initial visual acuity (90% less than count fingers), whereas those with branch retinal artery occlusion (BRAO) had better visual acuity (63.6% better than 20/40). Systemic arterial hypertension (HTN) was the most common associated risk factor. Carotid stenosis was found in 50% of cases, leading to endarterectomy in nine patients (6.9%), while an underlying cardiac cause was implicated in 14% of cases. Giant-cell arteritis was diagnosed in five patients (3.8%). Workup of RAO may detect treatable cardiovascular and systemic conditions, allowing prevention of further ocular recurrence or stroke. Authors have concluded that etiologic workup of retinal arterial occlusion can diagnose potentially treatable underlying systemic conditions, such as giant-cell arteritis, cardiac conditions, and extracranial cerebrovascular disease. Giant-cell arteritis has to be ruled out at the acute phase, while the role and timing of semi-urgent testing (supra-aortic Doppler echography, echocardiography, electrocardiography, lab workup) or delayed testing (transesophageal echocardiography, brain imaging) have yet to be determined.

Grayson et al. [15] reported on their efforts to compare patterns of arteriographic lesions of the aorta and primary branches in patients with Takayasu's arteritis (TAK) and giant-cell arteritis (GCA). Patients were selected from two North American cohorts of TAK and GCA. The frequency of arteriographic lesions was calculated for 15 large arteries. Cluster analysis was used to derive patterns of arterial disease in TAK versus GCA and in patients categorized by age at disease onset. Using latent class analysis, computer-derived classification models based upon patterns of arterial disease were compared with traditional classification. As a result, arteriographic lesions were identified in 145 patients with TAK and 62 patients with GCA. Cluster analysis demonstrated that arterial involvement was contiguous in the aorta and

usually symmetric in paired branch vessels for TAK and GCA. There was significantly more left carotid ($p = 0.03$) and mesenteric ($p = 0.02$) artery disease in TAK and more left and right axillary ($p < 0.01$) artery disease in GCA. Subclavian disease clustered asymmetrically in TAK and in patients ≤55 years at disease onset and clustered symmetrically in GCA and patients >55 years at disease onset. Computer-derived classification models distinguished TAK from GCA in two subgroups, defining 26% and 18% of the study sample; however, 56% of patients were classified into a subgroup that did not strongly differentiate between TAK and GCA. Authors have concluded that strong similarities and subtle differences in the distribution of arterial disease were observed between TAK and GCA. These findings suggest that TAK and GCA may exist on a spectrum within the same disease.

Furuta et al. [16] published in 2015 a study on Takayasu's arteritis (TAK) and giant-cell arteritis (GCA) as two major variants of large vessel vasculitis (LVV). The frequent involvement of large vessels in GCA has raised the possibility that TAK and GCA should be regarded as one disease. By detailed phenotyping of a single-center cohort, authors aimed to define the differences between TAK and GCA. Forty-five patients (23 TAK, 22 GCA) were identified. Baseline characteristics, clinical symptoms, laboratory data, enhanced computed tomography/magnetic resonance imaging, treatments, and clinical courses were retrospectively assessed with descriptive statistics. In addition, latent class analysis of the 45 patients was performed to explore phenotypic differences. Patients with GCA had more frequent headache ($p < 0.01$), higher C-reactive protein levels ($p = 0.01$), and higher erythrocyte sedimentation rates ($p = 0.03$) than did patients with TAK at diagnosis. With the exception of subdiaphragmatic lesions, the distributions of vessel lesions were not different between TAK and GCA. However, focusing on subclavian and carotid arteries, long tapered-type stenotic lesions were more frequent in GCA than in TAK ($p < 0.01$). The proportion of patients without relapse was higher in GCA (60%) than in TAK (22%, $p = 0.01$). Latent class analysis also divided patients with LVV into two separate groups consistent with TAK and GCA. Authors concluded that the differences observed in clinical symptoms, inflammatory markers, radiological findings, and clinical courses suggested that TAK and GCA were two different diseases. Latent class analysis supported these results. The shape of stenotic lesions in the subclavian and carotid arteries is a useful discriminator between TAK and GCA.

Kermani et al. [17] aimed in 2015 to compare clinical and imaging characteristics of patients with giant-cell arteritis (GCA) and upper extremity (UE) arterial involvement to patients with Takayasu's arteritis (TAK). A cohort of patients seen at the Mayo Clinic with TAK diagnosed between 1984 and 2009 and a cohort of patients with GCA and UE arterial involvement diagnosed between 1999 and 2008 were studied. The result was that the TAK cohort consisted of 125 patients (91% female); the mean age (±SD) at diagnosis was 30.9 (±10) years. The cohort of patients with GCA and UE involvement comprised of 120 patients (80% female); the mean age (±SD) at diagnosis was 67.8 (±7.5) years. The mean time from onset of symptoms to diagnosis was significantly longer in TAK (3.2 years) than GCA (0.5 years), $p < 0.001$. UE claudication was reported in 40% with TAK and 53% with GCA, $p = 0.04$. UE blood pressure discrepancy was present in 65% with TAK

versus 28% with GCA, $p < 0.001$. Involvement of the thoracic aorta, abdominal aorta, carotid arteries, innominate artery, mesenteric artery, and left renal artery was more frequently observed in TAK ($p < 0.05$). Among patients with luminal changes of the thoracic aorta, stenotic/occlusive lesions were predominant in TAK (81% compared to 0% in GCA), whereas aneurysmal disease was more common in GCA (100% compared with 19% in TAK, $p < 0.001$). Authors concluded that patients with GCA and UE involvement differ from patients with TAK in clinical and imaging characteristics. Aortic aneurysms were more common in GCA, while stenotic changes of the aorta were more common in TAK, suggesting different pathophysiologic mechanisms or vascular responses to injury.

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PMR and GCA Case Reports

20

Manfred Herold

Abbreviations

CRP	C-reactive protein
DM	Diabetes mellitus
ESR	Erythrocyte sedimentation rate
FGT	Female genital tract
GCA	Giant cell arteritis
GP	General practitioner
MRI	Magnetic resonance imaging
PMR	Polymyalgia rheumatica
TAB	Temporal artery biopsy

20.1 Case Report 1

Typical patients suffering from a disorder that for the first time is named polymyalgia rheumatica [1].

In 1957 the term "polymyalgia rheumatica" was recommended as a descriptive label for conditions we find in patients nowadays still defined as PMR [2, 3].

Twelve cases are described with continued observation over a period of 1–10 years. The symptoms were suggestive of a rheumatoid disease, but associated clinical signs usually could not be found. The onset was characterized as widespread muscular pain and described as sudden as the familiar stiff neck. The site of

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onset was either in the neck and shoulders or in the gluteal regions and thighs. In all cases, the muscle groups of the trunk and limbs successively became affected, and ESR was always elevated and often extremely high. Radiographic appearance of the hands was within the normal range and did not show any erosions.

This paper was written more than 60 years ago, but is still worth reading. The symptoms are well described and were observed over years. Steroids were not available and treatment was symptomatic with available pain killers like phenylbutazone and aspirin. Nevertheless, patients showed slow but spontaneous improvement, and over a period of years, some patients experienced complete remission. It was concluded that prognosis is good.

It is also mentioned that of the 12 described patients, two were men and 10 women, their ages at onset ranging from 46 to 68 years. The incidence in elderly persons was assumed. The author's final statement "… until more is known about it I suggest the term 'polymyalgia rheumatica' is remarkable."

20.1.1 Conclusion

In this first report on patients with PMR, the typical symptoms are described in detail; the elevated ESR, the prevalence in elderly persons, and the higher incidence in females are mentioned. The term recommended for these newly reported clinical features was obviously perfect precisely the way it was coined for the first time more than 60 years ago. Since then it has never changed!

20.2 Case Report 2

A typical patient with GCA [4].

A 73-year-old male presented with sudden onset of a 2-day history of severe left-sided headache. He described the headache as dull and throbbing, predominantly localized in the frontal and temporal areas on the left side, radiating down to the left side of the neck. On further examination, an exquisitely tender left temporal artery with mild temporal artery beading was palpated. On physical examination no other abnormalities could be found. A complete vascular examination was performed, which did not reveal any upper extremity pulse loss or subclavian, carotid, or axillary bruits. Computed tomography of the head ruled out any space-occupying or hemorrhagic lesions.

A full blood cell count showed a normal white cell count with only positive findings of an elevated ESR (27 mm/h) and a slightly elevated CRP level (10 mg/L). The patient was urgently prescribed 60 mg (0.75–1 mg/kg) of prednisolone as per hospital protocol, and during treatment he underwent regular follow-up to monitor for complications of high-dose steroid therapy. He experienced symptomatic relief within 24 h of initiation of steroid therapy.

Temporal artery biopsy was done soon after the steroid therapy was initiated. Histological signs were consistent with an inflammatory response, which is responding effectively to steroid therapy.

20.2.1 Conclusion

The diagnosis of temporal arteritis requires a high degree of suspicion as it may manifest in a variety of clinical features. The presence of characteristic clinical symptoms is increasingly suggestive of GCA and should still trigger initiation of treatment for GCA, even if ESR is only mildly elevated.

20.3 Case Report 3

PMR with bilateral subclavian artery stenosis [5].

A 66-year-old woman presented with proximal muscle pain and stiffness of 1 year's duration. The patient also reported acute onset of tingling with bluish discoloration in the nail beds and fingertips of her left hand, exacerbated with overhead activity. Physical examination revealed warm hands and good capillary refill in all digits despite a diminished right radial artery pulse and nonpalpable left radial artery pulse. Laboratory test results showed a normal complete blood cell count, elevated ESR (47 mm/h) and CRP level (32.4 mg/L), negative rheumatoid factor and antinuclear antibody, as well as normal creatine phosphokinase. Polymyalgia rheumatica was diagnosed, and the patient was started on prednisone 10 mg twice daily. There was significant improvement in her proximal arthralgias and myalgias, but left arm claudication persisted. Doppler ultrasound of the upper extremities revealed bilateral moderate (50%–74%) stenosis of the subclavian, axillary, and brachial arteries.

Although the patient had no cranial symptoms, giant cell arteritis was suspected to be the cause of occlusive vasculopathy. Treatment with prednisone 60 mg daily showed dramatic improvement in left arm symptoms.

Some weeks later the patient underwent angiography followed by angioplasty and stenting of the left subclavian artery. Postoperatively, the patient was administered aspirin because of intolerance of other oral anticoagulants.

The upper extremity arterial Duplex ultrasound revealed a patent left subclavian stent. The patient was doing well, maintained with an average dose of 5 mg of prednisone per day.

Some months later she presented with return of left arm claudication, discoloration, and absent left radial artery pulse. Noninvasive vascular testing demonstrated severe narrowing of the subclavian artery distal to the left subclavian stent. Vasculitis, secondary to giant cell arteritis, was assumed, evidenced by recurrent occlusive disease in the upper extremities. Steroid treatment was decided on for further disease control.

20.3.1 Conclusion

Physicians should be vigilant when assessing patients with PMR. The challenge is to recognize atypical cases presenting with occlusive vasculopathy, but lacking cranial symptoms suggestive of GCA.

20.4 Case Report 4

GCA and scalp necrosis [6].

A 77-year-old Caucasian male with a background history of hypertension and atrial fibrillation presented with a 4-week history of generalized headache, jaw claudication, and a large necrotic area over his scalp. He denied any visual loss or systemic symptoms. He had initially presented to his GP with a black painful nodule near the superior temporal line that was thought to be a ruptured superficial blood vessel. This had developed into a large, painful, and bilateral necrotic scalp ulcer on admission to hospital. Examination also revealed scalp tenderness and impalpable temporal arteries. Blood tests showed an elevated CRP level (66 mg/L) and ESR (74 mm/h).

Under treatment with high doses of prednisolone orally (60 mg once daily), GCA was improving both in his clinical symptoms and his inflammatory markers.

20.4.1 Conclusion

Prompt diagnosis and treatment with steroids prevented progression of the scalp necrosis and other catastrophic complications such as blindness and stroke.

20.5 Case Report 5

GCA restricted to limb arteries [7].

In a relevant fraction of cases, GCA may affect non-cranial vessels, specifically the ascending aorta and its main tributaries brachiocephalic, left common carotid, and left proximal subclavian arteries. Occasionally, GCA may involve more distal vessels, such as distal subclavian, brachial, axillary, iliac, or femoral arteries, leading to intermittent limb claudication and other vascular symptoms. Rarely, GCA may be restricted to the limb arteries without typical temporal artery and aorta involvement.

Three cases have been described. A previously healthy 78-year-old man had a 6-month history of bilateral, progressive numbness and hypoesthesia of the hands, associated with claudication of the upper limbs. He denied systemic and craniocervical symptoms. A 69-year-old woman with a history of PMR and diabetes mellitus presented with pelvic pain worsened by walking. She also denied systemic or temporal symptoms. Physical examination was unremarkable. A 77-year-old woman with pharmacologically treated hypertension came for consultation with a 3-month history of claudication of the upper limbs. Neither arterial bruits nor diminished peripheral pulses or asymmetric arm blood pressure was detected at physical examination. She denied cranial symptoms (headache of new onset, jaw claudication, scalp hyperesthesia, and visual symptoms), fever, fatigue, and weight loss. All three patients had elevated ESR and CRP level on admission.

Steroids were started immediately and resulted in successful reduction of symptoms.

20.5.1 Conclusion

The diagnosis of limb-restricted GCA is challenging also for the experienced immunologist. It has been rarely reported in the literature and probably has been overlooked.

If temporal biopsy and aortic imaging are negative for GCA in the appropriate clinical setting, limb-restricted GCA should be suspected. In patients older than 50 years, bilateral limb claudication, elevated ESR, suggestive vascular radiological findings, and, intriguingly, the absence of constitutional symptoms support the diagnosis.

20.6 Case Report 6

GCA of the female genital tract [8].

GCA has rarely been described in the female genital tract (FGT), with only 31 cases reported in the English-language literature. GCA of the FGT is generally discovered as an incidental finding in the hysterectomy and/or salpingo-oophorectomy specimen removed for some unrelated gynecologic condition.

An 83-year-old white female, with a previous medical history of hypertension, hyperlipidemia, osteoarthrosis, PMR, lumbago, and chronic obstructive pulmonary disease presented to the gynecology outpatient department with an episode of postmenopausal vaginal bleeding. She had elevated ESR (51 mm/h) and CRP level (39 mg/L). She denied any fever, fatigue, weight loss, headache, jaw claudication, or double vision. Her pelvic ultrasound revealed endometrial polyp, and she was scheduled for hysteroscopy, dilation and curettage, and polypectomy. On entering the uterine cavity, a polyp was removed from the right side of the endometrial cavity. The histopathologic evaluation of the polyp along with the curettage revealed well-differentiated endometrioid adenocarcinoma. Interestingly, the histologic examination revealed a granulomatous arteritis involving many small- to medium-sized arteries of the cervix, myometrium, bilateral fallopian tubes, and ovaries. Transmural inflammation was centered around the inner media and outer intima and composed of lymphocytes, plasma cells, histiocytes, and multinucleated giant cells. There was disruption of the internal elastic lamina with giant cells and epithelioid histiocytes lying closely apposed to the fragmented elastic fibers. The involved arterial wall was thickened with marked luminal narrowing. There was no leukocytoclastic vasculitis, neutrophil-rich inflammatory infiltrate, fibrinoid necrosis of the vessel wall, or extravascular necrosis. Infective etiology was ruled out with the help of special stains for microorganisms.

The patient was started on rituximab and was also scheduled for temporal artery biopsy (TAB). Histologic examination of bilateral TAB revealed GCA with similar histologic features as in the genital organs. Corticosteroid therapy was initiated with improvement in her PMR symptoms. Methotrexate was given for some time to help taper corticosteroid therapy and prevent relapse. Treatment response was monitored by sequential measurements of ESR and CRP as well as for any clinical signs. The patient is doing well after 3 years of follow-up with normal ESR and CRP levels and with no need for steroids.

20.6.1 Conclusion

GCA of the FGT is an exceptionally rare occurrence in the small- and medium-sized arteries of the FGT of postmenopausal elderly women mostly and may either be part of a generalized GCA or a localized incidental finding. Patients in whom GCA is unexpectedly discovered in the genital tract specimen should be thoroughly investigated for involvement of other sites. TAB should be considered even in the absence of laboratory or clinical findings supporting systemic disease. Prompt and appropriate treatment should be initiated with systemic glucocorticoid if the findings suggest generalized disease or ischemic complication.

20.7 Case Report 7

PMR in married couples [9].

The etiology of PMR remains challenging although current knowledge supports the role of both genetic and environmental factors. Among these, there is evidence that infectious agents could trigger the disease's onset in some cases. The occurrence of PMR in both a husband and a wife supports the pathogenetic role of an environmental factor.

Two couples are described where PMR occurred in a partner a few months after PMR was diagnosed and successfully treated in the other partner.

A 68-year-old Caucasian man presented to the rheumatology outpatient clinic complaining of pain in his shoulders, pelvic girdle, and thighs with prolonged morning stiffness. The patient showed limited and painful mobility of the upper and lower limbs. The initial laboratory workup showed elevated ESR (91 mm/h) and CRP level (33.9 mg/L). The diagnosis of PMR was made. Under oral prednisone of 25 mg daily, prompt improvement occurred and the patient has experienced no disease relapse. About 1 year later, his spouse, a 67-year-old Caucasian housewife, was referred to the rheumatology outpatient clinic because of pain in the shoulder girdle and pelvic girdle associated with prolonged morning stiffness lasting some weeks. She also met all diagnostic criteria for PMR and was successfully treated with oral steroids. The couple had been married for more than 20 years, they were not blood relatives, and had always lived in a rural area. They denied previous exposure to any potential environmental risk factors for PMR, including infectious agents. Notably, the husband used to have an influenza vaccination every year and reported having received his last flu vaccination 2 months before onset of the disease, while his wife received no flu vaccination.

A second couple was described, where PMR appeared in the husband some months after PMR and GCA were successfully treated in his wife. In addition to these two couples in Italy, a literature research revealed reports of seven cases of PMR in married couples living in Europe, the United States, and the Middle East. In two cases, a member of the couple presented with associated GCA; in three cases both husband and wife presented with PMR and GCA. Two cases of isolated GCA in conjugal pairs are also reported in the literature.

20.7.1 Conclusion

The occurrence of PMR in both a husband and a wife supports the idea of a possible pathogenetic role of an environmental factor.

20.8 Case Report 8

GCA and PMR, an ophthalmic emergency [10].

The occurrence of GCA in the setting of PMR is not uncommon. It is imperative to recognize the symptoms and signs of GCA in this setting as treatment of PMR with low-dose corticosteroids will not protect the patient from the blinding consequences of GCA.

Mrs. NB was referred for urgent ophthalmic review. Her right eye had a relative afferent pupillary defect, and her visual fields to confrontation demonstrated global field loss. The right temporal artery was tender and showed reduced pulsatility as compared to the left side. Examination of the anterior segment of the eye was otherwise normal for both eyes. Fundoscopy revealed a pale and swollen optic nerve head in the right eye. Investigations into previous ESR readings demonstrated that they had been rising over the past 3 months and became elevated at 91 mm/h 2 months before presentation. The CRP level taken 1 month before presentation was also elevated at 100 mg/L. These results and the clinical findings led to the provisional diagnosis of GCA. Mrs. NB was admitted to the hospital and started on a 3-day course of high-dose intravenous methylprednisolone (1 g) in an effort to prevent bilateral visual loss. Oral prednisolone (55 mg, 1 mg/kg) was then commenced before discharge. The temporal artery biopsy performed 2 days after admission revealed histological features consistent with GCA. She was seen 3 weeks later in the outpatient clinic to assess her ongoing steroid therapy and to add the steroid-sparing agent methotrexate to her regimen. Her ESR had dropped further to 26 mm/h. However, her visual acuity remained poor for hand movements only. Her other symptoms of GCA had resolved.

20.8.1 Conclusion

GCA is a preventable cause of blindness and can commonly occur in patients with PMR.

20.9 Case Report 9

GCA with uveitis [11].

GCA may present with unusual clinical symptoms, which when initially not recognized may result in adverse clinical outcome.

A 76-year-old man with a history of pseudophakia and exudative macular degeneration, treated with intravitreal bevacizumab injections, presented with temporal

headache and jaw pain, decreased vision at the counting finger level, and right eye pain for 4 months. He reported no episodes of fever or malaise. A disciform macular scar was noted on initial presentation. However, vitreous inflammation led to a presumptive diagnosis of endophthalmitis followed by prompt pars plana vitrectomy with vitreous biopsy, vitreous culture, and intravitreal antibiotics. Cultures and cytology were negative for infectious organisms and malignancy.

Posterior segment inflammation precluded a clear view of the process, and B scan ultrasonography demonstrated scleral thickening suggestive of posterior scleritis. Review of systems was positive for generalized fatigue and diffuse headache in addition to right eye redness and pain. Complaints of headache prompted testing for ESR and CRP. Both were elevated, measuring 70 mm/h and 58 mg/L, respectively. Temporal artery biopsy revealed an intense mixed inflammatory infiltrate involving all three layers of the vessel wall. The infiltrate was composed of a mixture of lymphocytes, plasma cells, histiocytes, and giant cells. Fibrinoid necrosis with neutrophils was noted. Luminal occlusion with recanalization was also evident. Verhoeff–van Gieson stain highlighted an extensively disrupted and focally obliterated internal elastic lamina. A diagnosis of GCA was rendered.

The patient was placed on high-dose oral prednisone and topical prednisolone acetate. His headache and jaw pain dramatically improved in the first 24 h and promptly resolved. ESR and C-reactive protein normalized. His scleritis quickly responded to treatment. His findings were significantly improved in 1 month and resolved by 2 months. Follow-up 5 months after diagnosis of GCA showed no recurrence of scleritis on a dose of only 5 mg prednisone daily, and ophthalmic examination demonstrated resolution of intraocular inflammation and scleritis.

20.9.1 Conclusion

Awareness that posterior uveitis and scleritis may be the presenting symptoms of GCA should prompt clinicians to ask about other symptoms of GCA and consider obtaining sedimentation rate, C-reactive protein, and temporal artery biopsy in select patients.

20.10 Case Report 10

GCA and cranial nerve palsy [12].

GCA mainly affects white people, but can occur worldwide. It is rare in Asians. In Asian cases, GCA has been more difficult to diagnose because of its low prevalence and atypical manifestations, as in this case with persistent multiple cranial nerve palsy and reversible proptosis.

A 74-year-old male with diabetes mellitus (DM) developed newly occurring headache, which interrupted his daily activities and sleep patterns for 1 month. It was localized over the bilateral temporal area and described as a tight feeling. Headache duration was all day long. Neither coincident nausea nor vomiting was reported.

General malaise and anorexia were also noted. Physical examination demonstrated a prominent but non-tender temporal artery over the right scalp. Neurological examination did not disclose any abnormality. Laboratory testing was remarkable for an elevated ESR (90 mm/h). Neither visual impairment, jaw claudication, nor polymyalgia rheumatica was noted during the first visit. Cranial CT was unremarkable. Temporal artery biopsy (TAB) was suggested, but the patient refused it because of religion and traditional culture. Only low-dose prednisolone (30–40 mg daily) was prescribed initially because of insufficient evidence of GCA and the possible side effect of high-dose corticosteroid therapy, particularly in an older patient with DM. More severe tension-like headache with proptosis, complete ophthalmoplegia, and decline of visual acuity in the right eye were noted 1 month later. Neurological examination revealed abducens nerve palsy, oculomotor nerve palsy, and an afferent papillary defect in the right eye. The pupil was isochoric, visual field was intact, and optic disk was normal. Cranial magnetic resonance image study was unremarkable. TAB about 1 month after the onset of symptoms demonstrated subintimal fibrosis and partial destruction of the vessel wall with inflammatory infiltrate. The diagnosis of GCA was thus made. Prednisolone 60 mg/day was initiated immediately.

Proptosis disappeared 1 week after initiation of steroid therapy. Abducens nerve palsy, oculomotor nerve palsy, and optic neuropathy remained unchanged 2 months after high-dose corticosteroid therapy.

20.10.1 Conclusion

GCA can have atypical clinical manifestations, including multiple cranial nerve palsy and reversible proptosis, among Asians. Headache may be the only initial presentation. When an older Asian patient presents with new-onset headache or chronic headache with a changed pattern, GCA should always be taken into consideration, even without other GCA-typical manifestations.

20.11 Case Report 11

GCA and stroke [13].

Stroke as a follow-up of GCA is less common (3–4%). Where stroke occurs, it may follow a fluctuant course corresponding to the severity of vasculitis.

A 63-year-old businessman presented to the emergency department with transient left arm weakness, expressive dysphasia, left facial droop, and muscle aches. He had sought out his GP 1 month previously with aches and pains: his GP diagnosed PMR and commenced steroid treatment with significant improvement. Before starting steroids, ESR was mildly elevated (22 mm/h), and CRP level was modestly elevated (46 mg/L). The patient discontinued steroids 2 days prior to admission, with relapse of symptoms.

On examination, reduced power was noted in his left hand with normal speech, no visual field abnormalities, and no facial droop. Investigations included a normal

ESR and CRP level. Computed tomography of the brain was normal, but magnetic resonance imaging of the brain and C spine showed a subacute right posterior parietal infarct with C3–C4 posterior disk bulge. His left upper limb weakness was not attributed to cervical myelopathy. Ultrasound of carotids showed no significant stenosis.

His symptoms were felt to be consistent with PMR and giant cell arteritis with concomitant stroke, and he was treated with high-dose aspirin and oral steroids. A TAB was scheduled. This was delayed secondary to worsening of left arm weakness, new left upper quadrantanopia, and left-sided neglect. A repeat MRI of the brain showed extension of the right middle cerebral infarct. The CRP level was elevated at 41 mg/L with normal ESR (6 mm/h). His steroid treatment was changed to high-dose intravenous methylprednisolone 1 g daily for 3 days; he subsequently continued on high-dose oral steroids (prednisolone 60 mg daily).

A temporal artery biopsy performed 2 weeks postadmission disclosed a small and fibrotic vessel. Histological examination confirmed giant cell arteritis.

The patient was discharged with mild weakness in his left upper limb and minimal functional limitations. He continued on low-dose aspirin and oral steroids.

20.11.1 Conclusion

Stroke is an uncommon but serious complication of GCA. Normal ESR and level of CRP do not preclude the diagnosis. Temporal artery biopsy should be considered for patients with stroke and symptoms suggestive of PMR.

20.12 Case Report 12

GCA and aortic dissection [14].

Giant cell arteritis may lead to catastrophic, large-vessel complications from chronic vascular wall inflammation without prompt diagnosis and treatment.

An 85-year-old woman with a four-year history of PMR and temporal arteritis diagnosed per biopsy 6 months previously presented with an acute sensation of neck tightness with radiation to her bilateral shoulders and the epigastrium. Within several hours of admission, the patient was found to be unresponsive and progressively bradycardic with depressed left ventricular function and an ejection fraction of 45%. She later developed a wide complex tachycardia before terminating in pulseless electrical activity. Subsequent autopsy showed extensive granulomatous inflammation with lymphocytes, giant cells, and elastic membrane destruction in the aorta and vertebrobasilar and coronary arteries. There was evidence of early aortic root and proximal segment dissection without aneurysmal dilatation, associated with mild pericardial effusion and left hemothorax. Despite mild, nonobstructive atherosclerosis, there was no evidence of coronary artery occlusion or myocardial focal ischemic changes. Additionally, no large artery stenosis was appreciated.

20.12.1 Conclusion

This case provides a rare histological example of spontaneous aortic dissection secondary to giant cell arteritis without preceding aneurysm and supports the hypothesis that inadequate treatment of GCA or PMR may predispose to development of aortic dissection. Aortic complications of GCA can be sudden and catastrophic, occurring years after symptomatic resolution. Normal ESR or CRP level in treated patients with PMR or GCA does not exclude the possibility of persistent aortic inflammation or associated risk of large-vessel dissection and rupture. Diagnosis and immediate corticosteroid treatment should be based on strong clinical suspicion, and surveillance imaging should follow initial assessment for large-vessel involvement.

20.13 Case Report 13

GCA and PMR after reexposure to a statin [15].

Adverse reactions to statins, such as myalgia, myositis, rhabdomyolysis, muscle weakness, and cramps with or without elevated serum creatine kinase levels, may occur. Furthermore, statins may also be associated with PMR.

A 78-year-old woman presented with muscle pain in the hips and shoulders and morning stiffness. She had a history of hypercholesterolemia treated with atorvastatin 10 mg/day for 9 months and hypertension treated with candesartan 8 mg/day and bisoprolol 2.5 mg/day. Laboratory studies revealed elevated ESR (61 mm/h). The patient was diagnosed with PMR and advised to discontinue atorvastatin therapy. Her symptoms gradually resolved. Five months after presentation, the ESR was normal (13 mm/h). Three years later her low-density lipoprotein cholesterol level was 4.5 mmol/L (174 mg/dL), and therapy with rosuvastatin, 5 mg twice weekly, was resumed. Symptoms of PMR recurred and progressed, and she reported visual disturbances. Temporal arteries were tender on palpation. Hematoxylin and eosin staining of a biopsy specimen of the temporal artery showed panarteritis comprising lymphocytes, neutrophils, eosinophils, and macrophages with giant cells. Intimal thickening with clear luminal narrowing was also noted. An ESR of 95 mm/h and a CRP level of 2381 nmol/L were found on laboratory study. GCA with PMR was diagnosed. Rosuvastatin therapy was discontinued, and the patient was treated with prednisolone, 40 mg/day, in which dosage was slowly tapered. Her symptoms abated over the next few months, the ESR and CRP level decreased to normal values, and prednisolone therapy was discontinued. A few months later, PMR and GCA relapsed. This time, relapse was not preceded by statin therapy. The patient again received corticosteroids, which resulted in a good response.

20.13.1 Conclusion

PMR should be suspected when a patient receiving statin therapy presents with myalgia of the hips and shoulders combined with morning stiffness.

20.14 Case Report 14

GCA and PMR after influenza vaccination [16].

Over a 6-year period, 20 patients were diagnosed with GCA/PMR, of whom 10/20 (50%) had received an influenza vaccination 20 days to 3 months before onset of the disease. Among this group of patients, eight had been given a diagnosis of GCA confirmed by biopsy, and two PMR. Two patients concomitantly suffered from GCA and PMR. Interestingly, all patients were female and previously healthy. Patient age at the time of diagnosis ranged between 64 and 80 years, with a median of 73.5. All temporal artery biopsies confirmed the diagnosis of GCA. All patients received steroid therapy for at least 24 months, with full clinical remission. Of note, one patient diagnosed with PMR following influenza vaccination was in clinical remission subsequent to steroid therapy when a relapse of her disease occurred 2 years later, following revaccination with seasonal influenza vaccination. The literature survey yielded seven isolated cases of PMR and four of GCA following influenza vaccination.

The interval between vaccine administration and onset of clinical manifestations ranged from a minimum of 1 day to a maximum of 3 weeks. Among patients with GCA, three developed the disease after influenza vaccination, being previously healthy subjects, whereas in one patient the disease manifested 6 months after administration of hepatitis B vaccine in a woman in remission after being diagnosed with PMR 2 years previously.

20.14.1 Conclusion

The incidence rate of postvaccination phenomena following influenza vaccination is still unknown, but the possibility that it can occur in the elderly population should be considered.

20.15 Case Report 15

GCA and amyloidosis [17].

Secondary amyloidosis can develop in a patient with seemingly quiescent GCA/PMR.

A 79-year-old woman presented to the rheumatology service with new-onset unilateral headache and prominence and tenderness of the left temporal artery.

The ESR (85 mm/h) and CRP level (40.9 mg/L) were elevated. She met four of the five American College of Rheumatology 1990 criteria for GCA: age > 50 years, new-onset headache, temporal artery abnormality, and ESR > 50 mm/h1. She denied symptoms of PMR, but she had anorexia and generalized fatigue that had been persistent for several years.

Subsequent investigations for GCA included left-side temporal artery biopsy of 1 cm and MRI of the scalp vessels with contrast. The temporal artery biopsy was negative for evidence of arteritis; however, the MRI showed abnormal enhancement in the superficial temporal artery in the postcontrast images. This finding was felt to be diagnostic of arteritis.

She was initially treated for GCA with prednisone 50 mg daily for 3 weeks, with complete resolution of her symptoms, which was slowly tapered to 15 mg daily as maintenance. Her ESR improved to a nadir of 23 mm/h. Some weeks later she had a relapse of her symptoms and was retreated with high-dose prednisone for 2 weeks with prompt resolution. Three weeks later she was admitted to hospital with shortness of breath and increasing peripheral edema, which was treated as COPD exacerbation. She was managed with prednisone 50 mg daily on slow taper, antibiotics, bronchodilators, and diuretics. Creatinine was 165 μmol/L, with a baseline of 94 μmol/L some months before. A 24 h urine protein collection showed a nephrotic-range proteinuria of 3.68 g, and angiotensin receptor blocker therapy was added.

She suffered a new acute renal failure (peak creatinine 282 μmol/L) 2 months later. Serum and urine protein electrophoresis were negative for M protein. Also negative were antinuclear antibody, rheumatoid factor, cytoplasmic and perinuclear antineutrophilic cytoplasmic antibody, antiglomerular basement membrane antibody, and hepatitis B and C serology.

Renal biopsy demonstrated nodules of acellular eosinophilic material that was periodic acid–Schiff negative, non-argyrophilic on Jones silver stain, green/orange on trichrome stain, and Congo-red positive. It had an apple-green appearance on polarized microscopy. Immunofluorescence showed isointense staining for kappa (2+) and lambda (3+).

On immunohistochemistry, amyloid A immunostain was strongly positive. Electron microscopy confirmed the findings, which were diagnostic of AA amyloidosis affecting the kidney. Review of the temporal artery biopsy was negative for amyloid. Bone marrow biopsy showed evidence of amyloid with no evidence of abnormal cell infiltrate.

At the time of diagnosis of AA amyloidosis, the patient had no symptoms of GCA or PMR. Her ESR was 73 mm/h with a CRP level of 35.4 mg/L. She was receiving 5 mg prednisone daily. Colchicine 0.6 mg daily was initiated, but was decreased to 0.3 mg daily due to diarrhea. At 4 months her creatinine had stabilized at 220 μmol/L, with a 24 h urine protein of 3.81 g.

20.15.1 Conclusion

This case raises the possibility of secondary amyloidosis developing in a patient with seemingly quiescent GCA/PMR, which highlights the need for screening with periodic serum creatinine measurement and urinalysis for protein. Colchicine may be effective in preventing or delaying progression of renal failure in AA amyloid.

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