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

J. Rovenský, M.D., D.Sc., F.R.C.P. (✉)
National Institute of Rheumatic Diseases, Piešťany, Slovakia

Department of Rheumatology, Faculty of Medicine, Slovak Medical University, Bratislava, Slovakia
e-mail: rovensky.jozef@gmail.com

I. Kozák
Jacobs Retina Center, University of California, San Diego, La Jolla, CA, USA

J. Rovensky et al. (eds.), *Polymyalgia Rheumatica and Giant Cell Arteritis*,
DOI 10.1007/978-3-319-52222-7_16

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

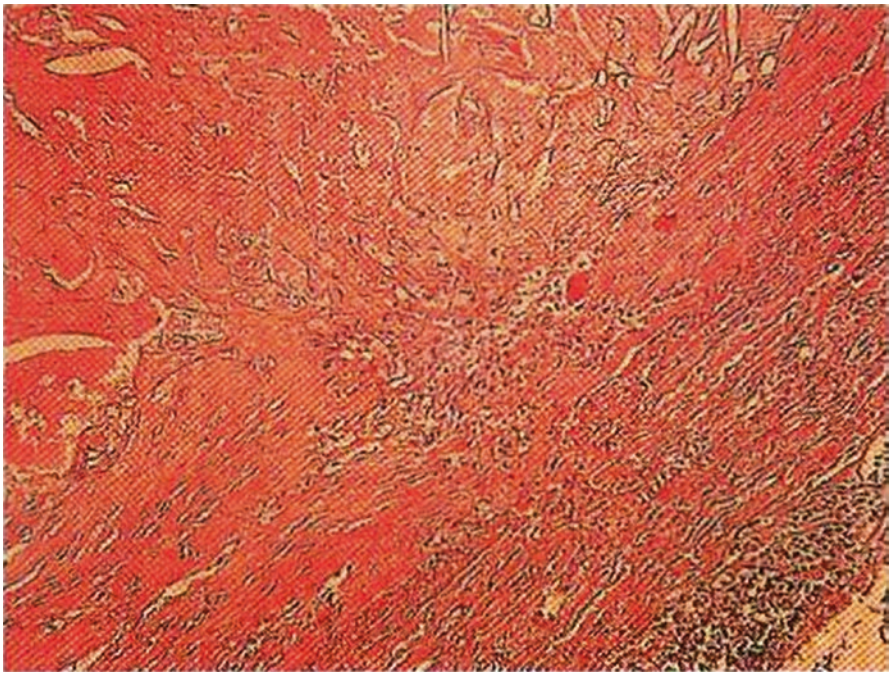

Fig. 16.1 Granuloma in the media of the abdominal aorta (hematoxylin and eosin (H&E) staining)

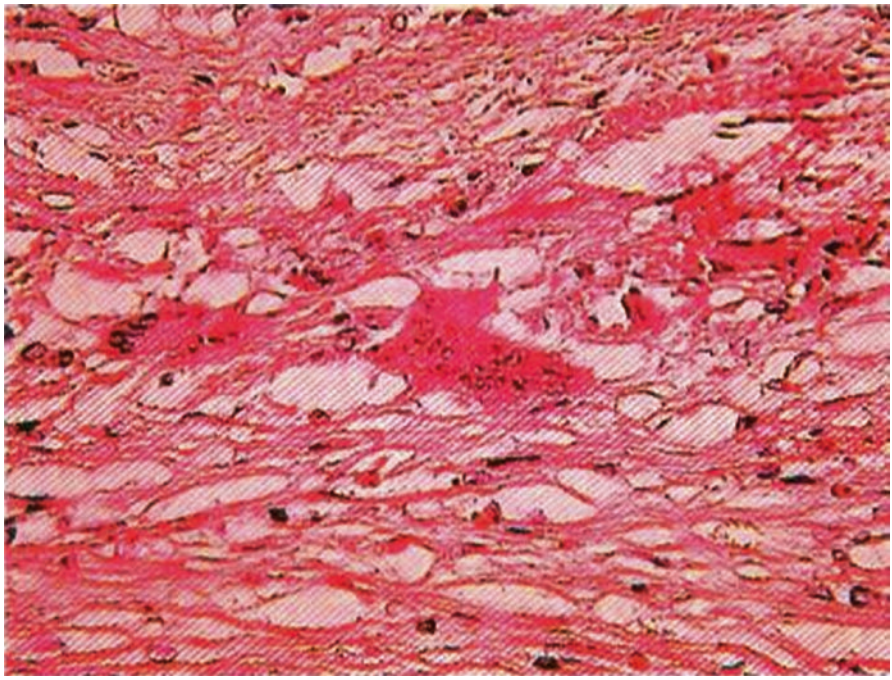

Fig. 16.2 Inflammatory infiltrate composed predominantly of histiocytes and plasma cells, not so many lymphocytes, and one giant multinucleated cell (hematoxylin and eosin (H&E) staining)

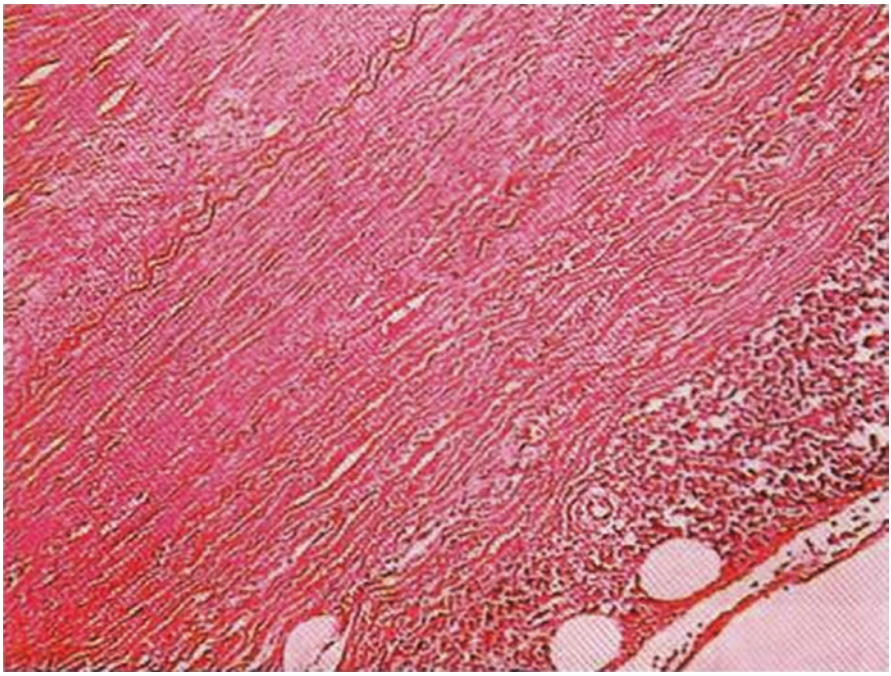

Fig. 16.3 Splitting and fragmentation of the internal elastic membrane (hematoxylin and eosin (H&E) staining)

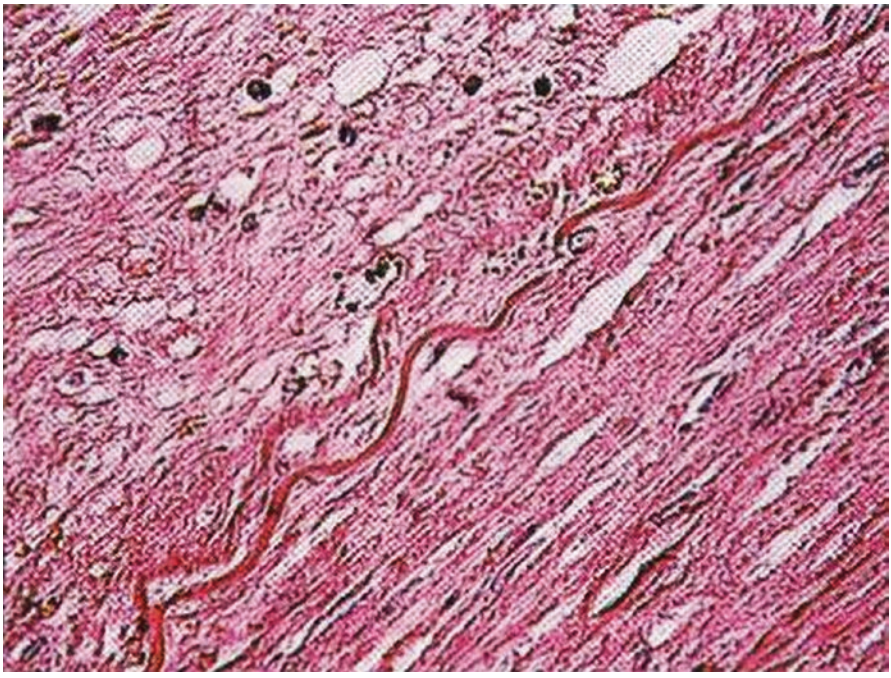

Fig. 16.4 Calcium powder in the internal elastic lamina

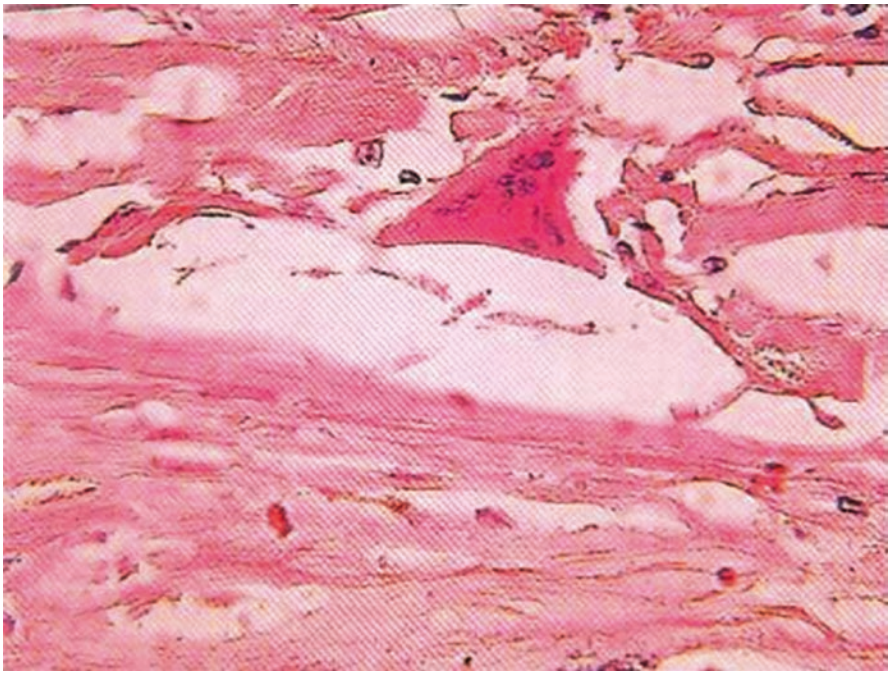

Fig. 16.5 A multinucleated giant cell. Aorta of an 86-year-old man (hematoxylin and eosin (H&E) staining)

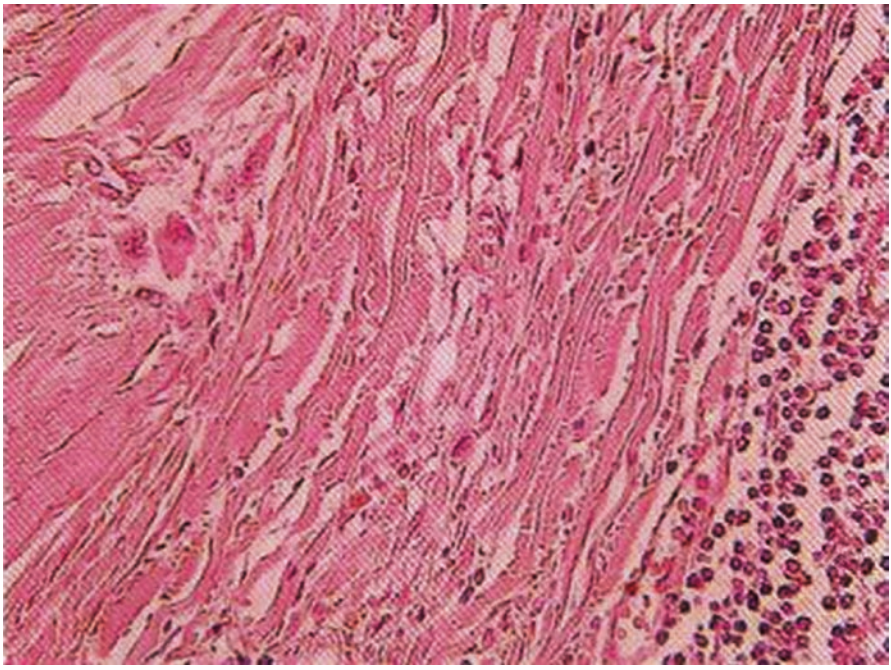

Fig. 16.6 Split internal elastic lamina. A multinucleated giant cell (hematoxylin and eosin (H&E) staining)

(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).

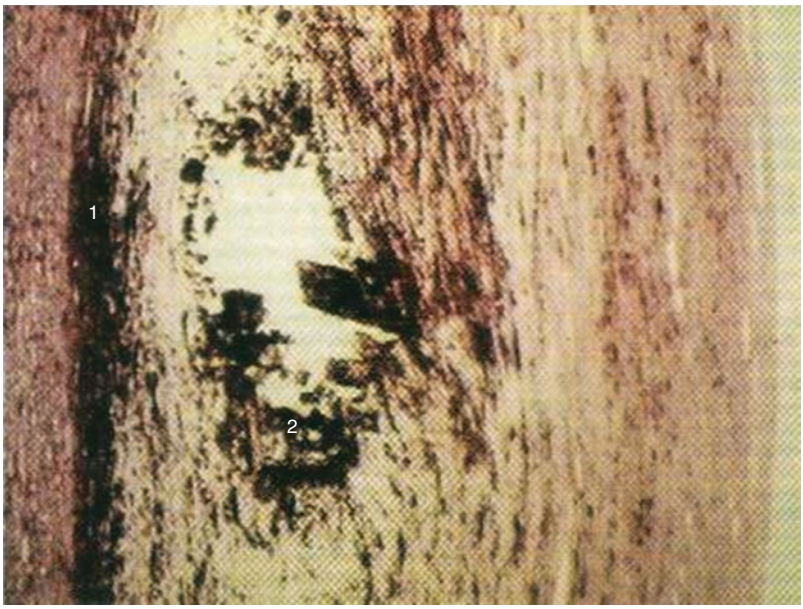

Fig. 16.7 Deposits of calcium (*1*) in the area of the internal elastic lamina and sclerotic plaque with calcium in the intima (*2*) (KOSSA+HE staining)

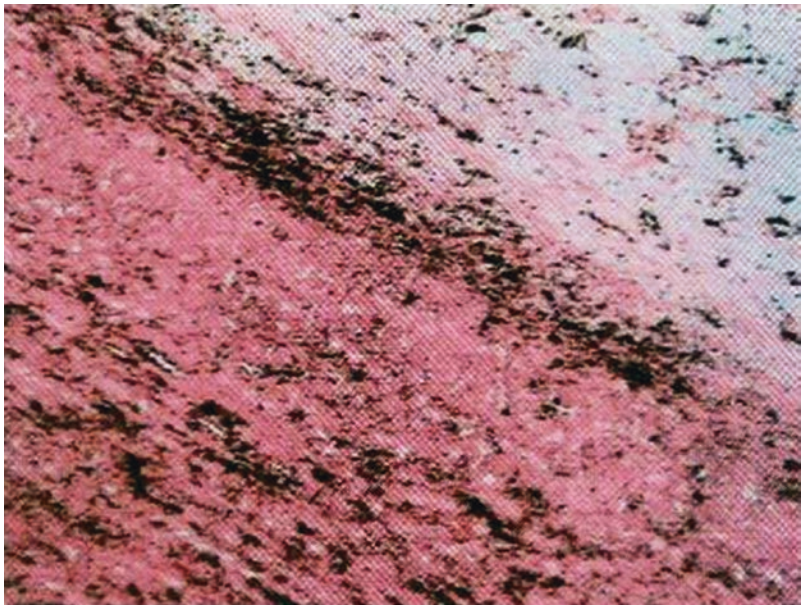

Fig. 16.8 Typical image of calcium powder in the internal elastic lamina (KOSSA+HE staining)

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).

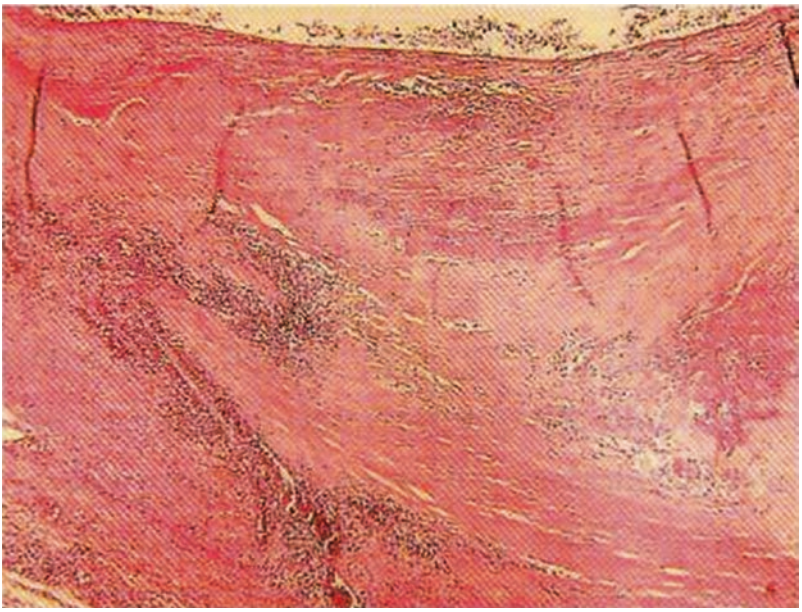

Fig. 16.9 Neovascularization in the aortic media of an 86-year-old man with GCA

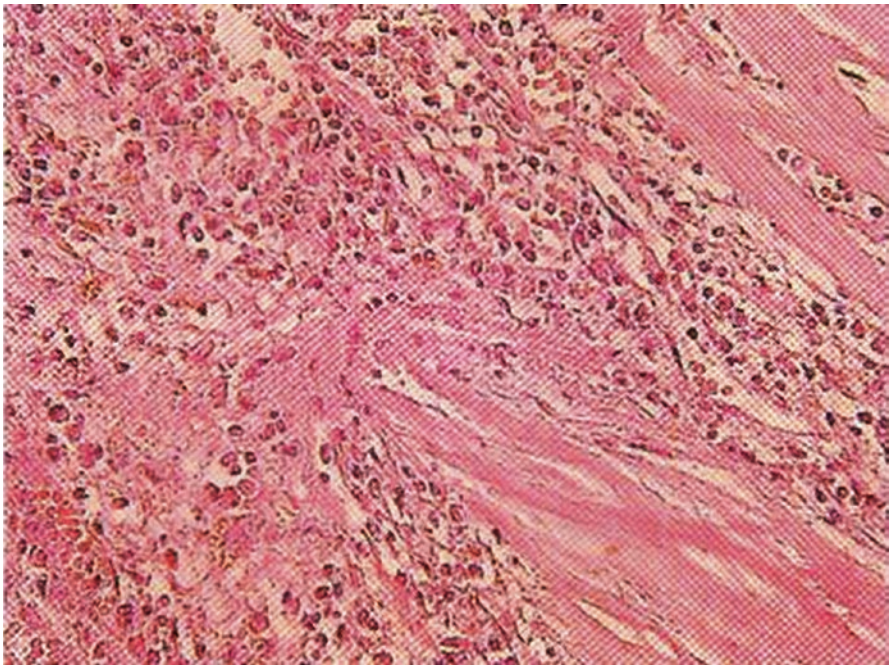

Fig. 16.10 Detail of neovascularization in the aortic media with inflammatory infiltration and destruction of elastic fibers

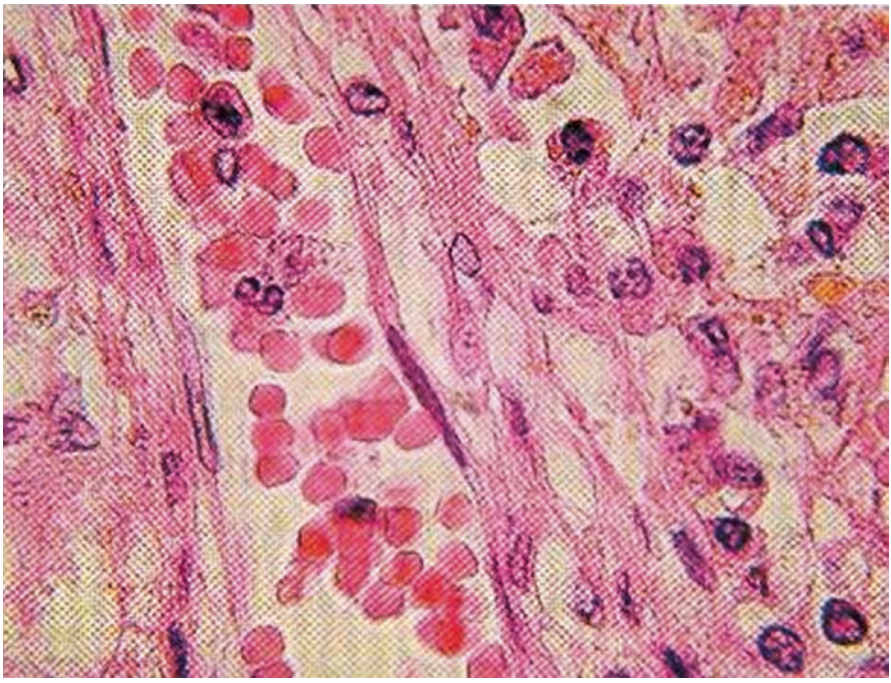

Fig. 16.11 Neovascularization—greater detail than in Fig. 17.14

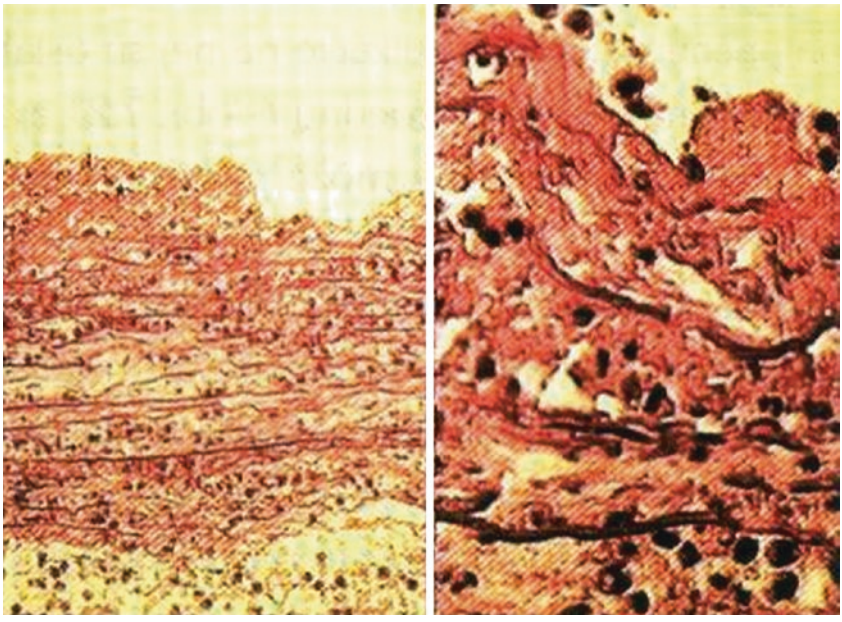

Fig. 16.12 Panarteritis with a mixed inflammatory infiltrate (hematoxylin and eosin (H&E) staining)

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

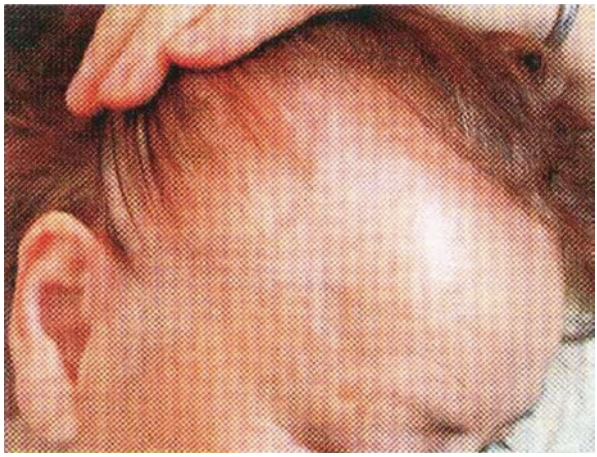

Fig. 16.13 Enlarged temporal artery in a female patient with GCA

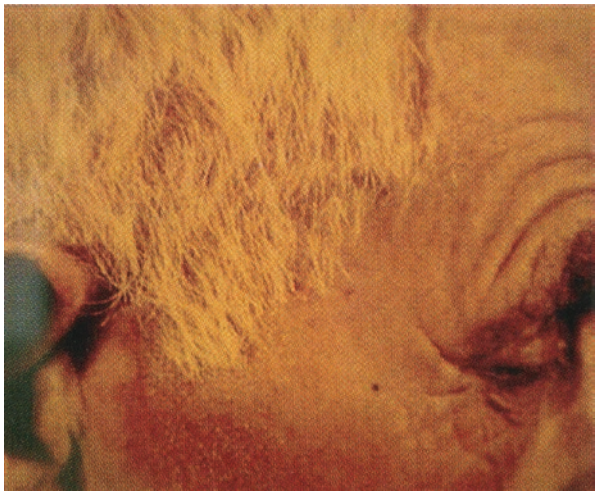

Fig. 16.14 A patient with histologically proven temporal arteritis

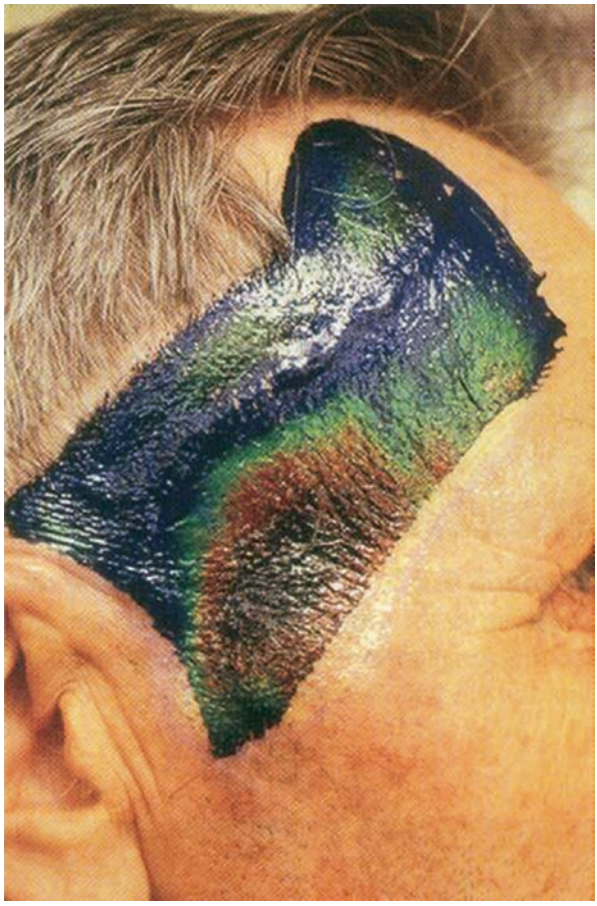

Fig. 16.15 Thermographic image of the temporal arteritis site showing increased temperature gradient in the area of superficial temporal artery

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

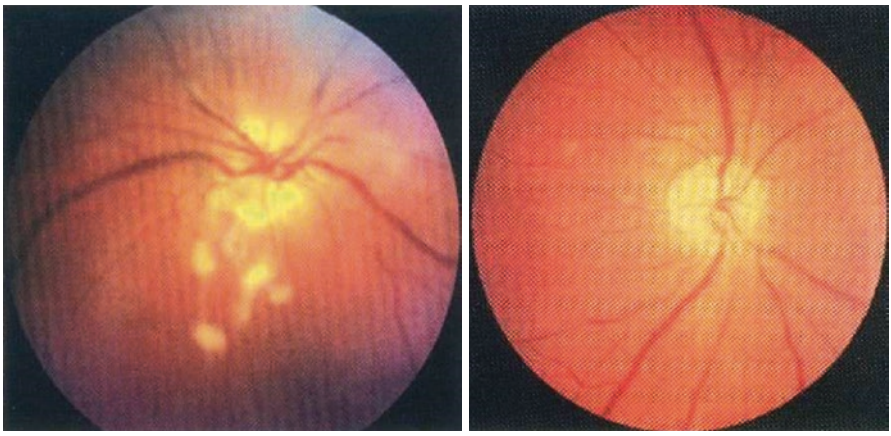

Fig. 16.16 GCA complications in our group of patients. *Left*—ischemic changes of optic nerve disc and retina of the right eye prior to corticosteroid treatment; *right*—fundus after corticotherapy. Treatment with high glucocorticoid doses saved the patients' sight

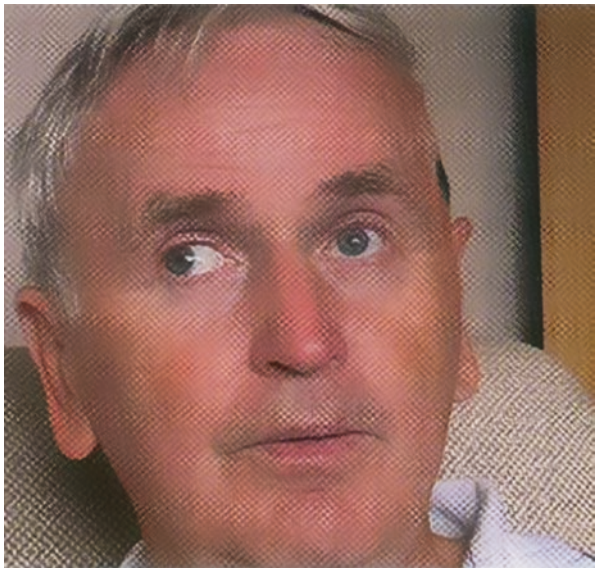

Fig. 16.17 GCA associated with oculomotor nerve palsy (convergence insufficiency)

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

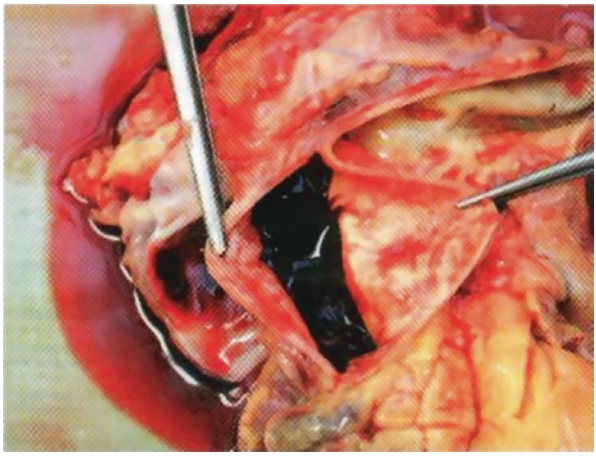

Fig. 16.18 Macroscopic image of the aortic arch showing a split aortic wall with blood clots

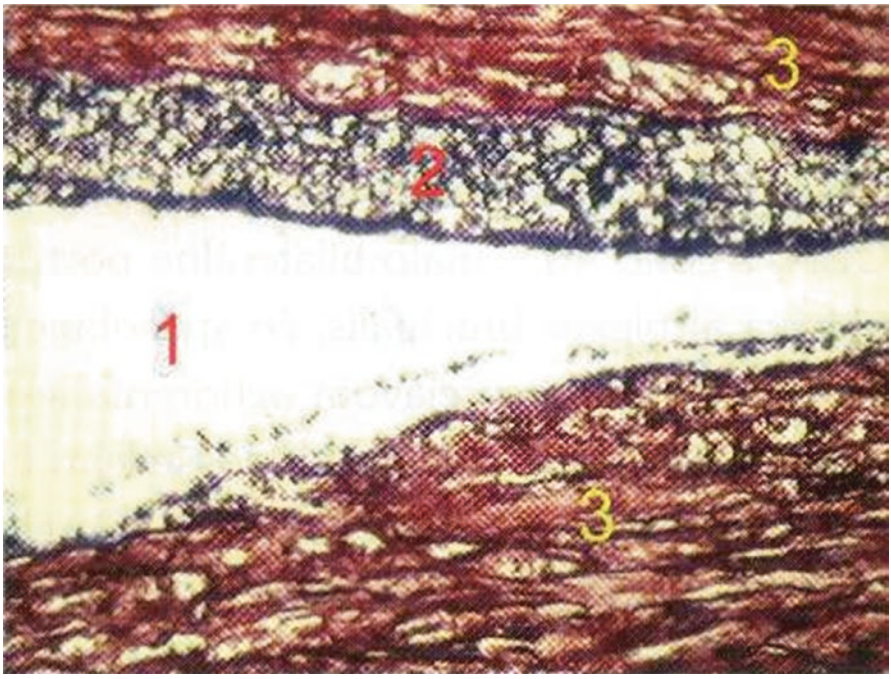

Fig. 16.19 Dissecting aneurysm of the aorta—dissection (*1*), fibrin (*2*), media (*3*) (phosphotungstic hematoxylin staining)

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

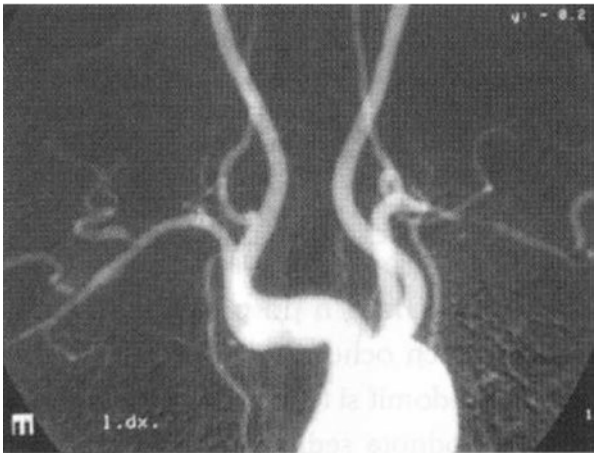

Fig. 16.20 Angiography of an 81-year-old female patient with GCA—stenotizing changes in arteries of both upper extremities

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

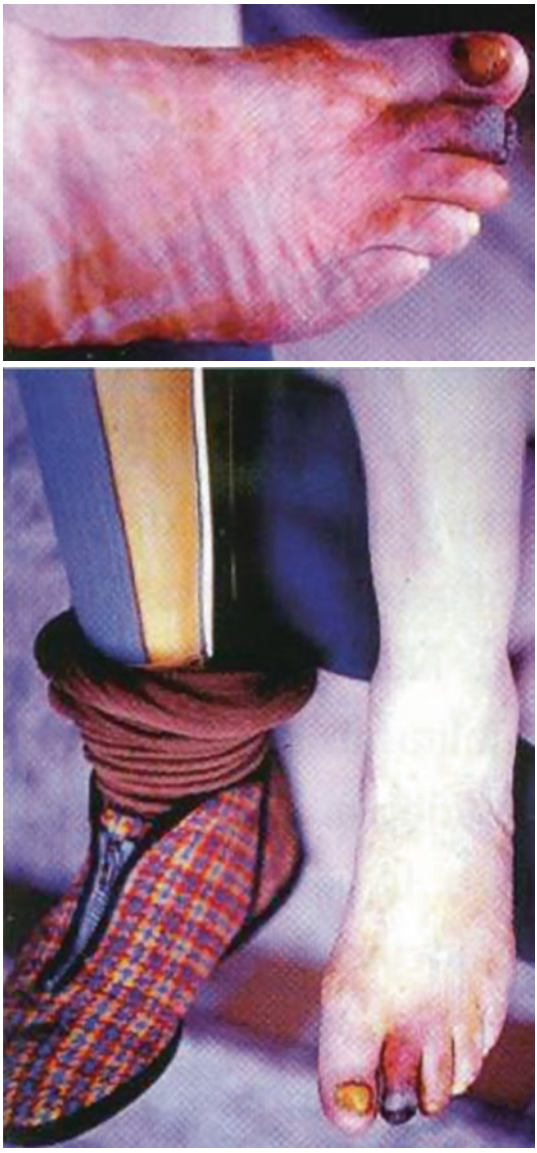

Fig. 16.21 GCA complications in our group of patients. Fatal consequences of PMR/GCA in histologically proven arteritis of peripheral blood vessels of lower extremities with a subsequent gangrene and amputation of the right lower leg and the condition of the left foot. After the last complication, the 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

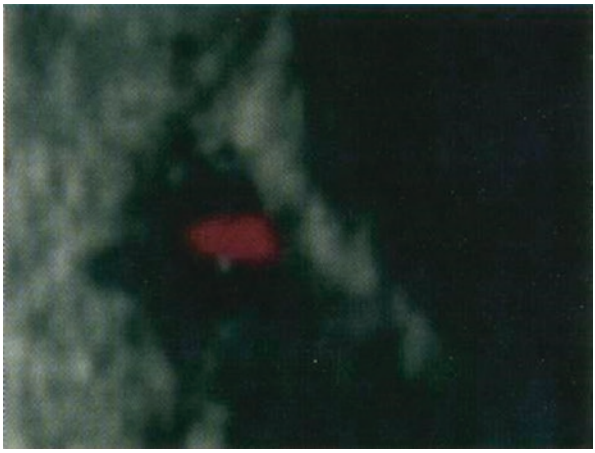

Fig. 16.22 Color Doppler ultrasonography finding and swelling of temporal artery with reduced flow rate (*red coding*) in a female patient with temporal arteritis (*cross section*)

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.

References

1. Smeeth L, Cook C, Hall AJ. Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990 to 2001. Ann Rheum Dis. 2006;65(8):1093–8.
2. Bengtsson BA. Giant cell arteritis. In: Ansell BM, Bacon PA, Lie JT, Yazici H, editors. The vasculitides. Science and practice. London: Chapman and Hall Medical; 1996. p. 171–80.
3. Lie JT. Coronary vasculitis. A review in the current scheme of classification of vasculitis. Arch Pathol Lab Med. 1987;111(3):224–33.
4. Weyand CM, Goronzy JJ. Pathogenetic principles in giant cell arteritis. Int J Cardiol. 2000;75(Suppl 1):S9–15.
5. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994;37(2):187–92.

6. Lie JT, Failoni DD, Davis DC. Temporal arteritis with giant cell aortitis, coronary arteritis, and myocardial infarction. Arch Pathol Lab Med. 1986;110(9):857–60.
7. Štvrtina S, Rovenský J, Galbavý S. Aneuryzma aorty ako príčina smrti pri obrovskobunkovej arteritíde. Rheumatologia. 2003;17(3):213–20.
8. Lie JT. Aortic and extracranial large vessel giant cell arteritis: a review of 72 cases with histopathologic documentation. Semin Arthritis Rheum. 1995;24(6):422–31.
9. Pipinos II, Hopp R, Edwards WD, Radio SJ. Giant cell temporal arteritis in a 17-years-old male. J Vasc Surg. 2006;43(5):1053–5.
10. Rovenský J, Tauchmannová H, Štvrtinová V, Štvrtina S. Príspevok k problematike juvenilnej temporálnej arteritídy. Rheumatologia. 2005;19(4):153–5.
11. Huston KA, Hunder GG, Lie JT, et al. Temporal arteritis. A 25 year epidemiologic, clinical and pathologic study. Ann Intern Med. 1978;88(2):162–7.
12. Bengtsson BA, Malmvall BE. The epidemiology of giant cell arteritis including temporal arteritis and polymyalgia rheumatica. Arthritis Rheum. 1981;24:899–904.
13. Narvaez J, Nolla-Sole JM, Valverde-Garcia J, et al. Sex differences in temporal arteritis and polymyalgia rheumatica. J Rheumatol. 2002;29:321–5.
14. Rovenský J, Tauchmannová H, Štvrtinová V, Štvrtina S, Duda J. Polymyalgia rheumatica a obrovskobunková arteritída, príspevok ku klinicko-laboratórnej syndro- mológii a terapii. Ces Revmatol. 2006;14(3):135–43.
15. Gran J. Some thoughts about the etiopathogenesis of temporal arteritis—a review. Scand J Rheumatol. 2002;31:1–5.
16. Lee SJ, Kavanaugh A. Autoimmunity, vasculitis and autoantibodies. J Allergy Clin Immunol. 2006;117(2):S445–50.
17. Hellmann DB. Immunopathogenesis, diagnosis, and treatment of giant cell arteritis, temporal arteritis, polymyalgia rheumatica, and Takayasu's arteritis. Curr Opin Rheumatol. 1993;5:25–32.
18. Imrich R, Bošák V, Rovenský J. Polymyalgia rheumatica a temporálna arteritída: vzťah hormónov k patogenéze. Rheumatologia. 2003;17(1):69–77.
19. Olsson A, Elling P, Elling H. Synchronous variations of the incidence of arteritis temporalis and polymyalgia rheumatica in different regions of Denmark; association with epidemics of *Mycoplasma pneumoniae* infection. Clin Rheumatol. 1994;13(2):384.
20. Perfetto F, Moggi-Pignone M, Becucci A, et al. Seasonal pattern in the onset of polymyalgia rheumatica. Ann Rheum Dis. 2005;64:1662–3.
21. Pacheco MJB, Amado JA, Lopez-Hoyos M, et al. Hypothalamic-pituitarity-ad- renocorticalis axis function in patients with polymyalgia rheumatica and giant cell arteritis. Semin Arthritis Rheum. 2003;32:266–72.
22. Narváez J, Bernard B, Diaz Torné C, et al. Low serum levels of DHEAS in untreated polymyalgia rheumatica/giant cell arteritis. J Rheumatol. 2006;33:1293–8.
23. Nordborg C, Nordborg E, Petursdottir V. The pathogenesis of giant cell arteritis: morphological aspects. Clin Exp Rheumatol. 2000;18(Suppl 20):S18–21.
24. Nordborg C, Nordborg E, Petursdottir V, Fyhr IM. Calcification of the internal elastic membrane in temporal arteries: its relation to age and gender. Clin Exp Rheumatol. 2001;19(5):565–8.
25. Weyand CM, Goronzy JJ. Pathogenetic mechanisms in giant cell arteritis. Cleve Clin J Med. 2002;69(Suppl 2):SII28–32.
26. Kaiser M, Younge B, Bjornsson J, et al. Formation of new vasa vasorum in vasculitis. Production of angiogenic cytokines by multinucleated giant cells. Am J Pathol. 1999;155(3):765–74.
27. Rovenský J, Tuchyňová A, Lukáč J. Polymyalgia rheumatica a temporálna arteritída. S. 1479–1483. In: Bernadič M, Duriš I, Hulín I, editors. Princípy internej medicíny 2. Bratislava: Slovak Academic Press; 2001. p. 3109.
28. Chew SSL, Kerr NM, Danesh-Meyer HV. Giant cell arteritis. J Clin Neurosci. 2009;16:1263–8.

29. Kale N, Eggenberger E. Diagnosis and management of giant cell arteritis: a review. Curr Opin Ophthalmol. 2010;21(6):417–22.
30. Murchinson AP, Gilbert ME, Bilyk JR, et al. Validity of the American College of Rheumatology criteria for the diagnosis of giant cell arteritis. Am J Ophthalmol. 2012;154:722–9.
31. Murphy EA, Capell H. Aortitis and large vessel vasculitides. In: Tooke JE, Lowe GDO, editors. A textbook of vascular medicine. London: Arnold; 1996. p. 287–94.
32. Chaouat D. Peripheral joint involvement in polymyalgia rheumatica. Rev Rhum. 1997;64:184–8.
33. Ceccato F, Roverano SG, Papasidero S, et al. Peripheral musculoskeletal manifestations in polymyalgia rheumatica. J Clin Rheumatol. 2006;12:167–71.
34. Evans JM, O'Fallon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis. A population-based study. Ann Intern Med. 1995;122(7):502–7.
35. Karger B, Fechner G. Sudden death due to giant cell coronary arteritis. Int J Legal Med. 2006;120(6):377–9.
36. Martin JF, Kittas C, Triger DR. Giant cell arteritis of coronary arteries causing myocardial infarction. Br Heart J. 1980;43(4):487–9.
37. Säve-Söderbergh J, Malmvall BE, Andersson R, Bengtsson BA. Giant cell arteritis as a cause of death. JAMA. 1986;255(4):493–6.
38. Polak P, Pokorný V, Štvrtina S, et al. Temporal arteritis presenting with paresis of the oculomotor nerve and polymyalgia rheumatica, despite a low erythrocyte sedimentation rate. J Clin Rheumatol. 2005;11(4):242–4.
39. Nesher G. Neurologic manifestations of giant cell arteritis. Clin Exp Rheumatol. 2000;18(Suppl 20):S24–6.
40. Achkar AA, Lie JT, Gabriel SE, et al. Giant cell arteritis involving the facial artery. J Rheumatol. 1995;22:360–2.
41. Nir-Paz R, Gross A, Chajek-Shaul T. Reduction of jaw opening (trismus) in giant cell arteritis. Ann Rheum Dis. 2002;61:832–3.
42. Caselli RJ, Hunder GG, Whisnant JP. Neurologic disease in biopsy-proven giant cell (temporal) arteritis. Neurology. 1988;38:352–9.
43. Garcia Vázques JM, Carreira JM, Seoane C, et al. Superior and inferior limb ischemia in giant cell arteritis: angiography follow up. Clin Rheumatol. 1999;18:61–5.
44. Dupuy R, Mercié P, Neau D, et al. Giant cell arteritis involving the lower limbs. Rev Rhum. 1997;64:500–3.
45. Le Hello C, Lévesque H, Jeanton M, et al. Lower limb giant cell arteritis and temporal arteritis: follow up of 8 cases. J Rheumatol. 2001;28:1407–11.
46. Tato F, Hoffmann U. Clinical presentation and vascular imaging in giant cell arteritis of the femoropopliteal and tibioperoneal arteries. Analysis of four cases. J Vasc Surg. 2006;44(1):176–82.
47. Huong DT, Andreu MR, Duhaut P, et al. Intra-alveolar haemorrhage in temporal arteritis. Ann Rheum Dis. 2003;62:189–90.
48. Gur H, Ehrenfeld M, Izsak E. Pleural effusion as a presenting manifestation of giant cell arteritis. Clin Rheumatol. 1996;15:200–3.
49. Hazleman B. Laboratory investigations useful in the evaluation of polymyalgia rheumatica (PMR) and giant cell arteritis (GCA). Clin Exp Rheumatol. 2000;18(Suppl 20):S29–31.
50. Churg J. Systemic vasculitis. In: Grishman E, Churg J, Needle MA, Venkataseshan VS, editors. The kidney in collagen-vascular diseases. New York: Raven Press; 1993. p. 213–50.
51. Martinez-Taboada VM, Blanco R, Rodriguez-Valverde V. Polymyalgia rheumatica with normal erythrocyte sedimentation rate: clinical aspects. Clin Exp Rheumatol. 2000;18(Suppl 20):S34–7.
52. Martinez-Taboada VM, Blanco R, Armona J, et al. Giant cell arteritis with the erythrocyte sedimentation rate lower than 50. Clin Rheumatol. 2000;19:73–5.

53. Salvarani C, Hunder GG. Giant cell arteritis with low erythrocyte sedimentation rate: frequency of occurrence in a population-based study. Arthritis Rheum. 2001;45:140–5.
54. Mowat AG. Polymyalgia rheumatica and giant cell arteritis. In: Warrell D, Cox TM, Firsth JD, editors. Oxford textbook of medicine, vol. 3. Oxford: Oxford University Press; 2003. p. 103–6.
55. Krisha R, Kosmorsky GS. Implications of thrombocytosis in giant cell arteritis. Am J Ophthalmol. 1997;124:103.
56. Ilan Y, Ben-Cherit E. Liver involvement in giant cell arteritis. Clin Rheumatol. 1993;12:219–22.
57. Hernandez-Rodriguez J, Garcia-Martinez A, Casademont J, et al. A strong initial systemic inflammatory response is associated with higher corticosteroid requirements and longer duration of therapy in patients with giant-cell arteritis. Arthritis Rheum. 2002;7:29–35.
58. Weyand CM, Fulbright JW, Hunder GG, et al. Treatment of giant cell arteritis: inter- leukin-6 as a biologic marker of disease activity. Arthritis Rheum. 2000;45:1041–8.
59. Uddhammar AC. Von Willebrand factor in polymyalgia rheumatica and giant cell arteritis. Clin Exp Rheumatol. 2000;18(Suppl 20):S32–3.
60. Chou C, Schumacher HR. Clinical and pathologic studies of synovitis in polymyalgia rheumatica. Arthritis Rheum. 1984;27:1107–17.
61. Lopez-Hoyos M, Ruiz de Alegria C, Blanco R, et al. Clinical utility of anti-CCP antibodies in the differential diagnosis of elderly-onset rheumatoid arthritis and polymyalgia rheumatica. Rheumatology (Oxford). 2001;43:655–7.
62. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of the giant cell arteritis. Arthritis Rheum. 1990;33(8):1122–8.
63. Jennette JC, Falk RJ, Bacon PA, et al. 2012 Revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Arthritis Rheum. 2013;65(l):1–11.
64. Joyce JW. Arteritis. In: Eastcott HHG, editor. Arterial surgery. Madrid: Churchill Livingstone; 1992. p. 211–22.
65. Epperly TD, Moore KE, Harrover JD. Polymyalgia rheumatica and temporal arteritis. Am Fam Physician. 2000;62:789–96.
66. Bird HA, Esselinckx W, Dixon A. An evaluation of criteria for polymyalgia rheumatica. Ann Rheum Dis. 1979;38:434–9.
67. Jones JG, Hazleman BL. Prognosis and management of polymyalgia rheumatica. Ann Rheum Dis. 1981;40:1–5.
68. Štvrtinová V, Rauová L, Tuchyňová A, Rovenský J. Vasculitis of the coronary arteries and atherosclerosis: random coincidence or causative relationship? In: Shoenfeld Y, Harats D, Wick G, editors. Atherosclerosis and autoimmunity. Amsterdam: Elsevier; 2001. p. 315–27.
69. Edmeads J. Headaches in older people. How are they different in this age-group? Postgrad Med. 1997;101:91–100.
70. Cohen MD, Abril A. Polymyalgia rheumatica revisited. Bull Rheum Dis. 2001;50:1–4.
71. Rovenský J, Leeb BF, Štvrtinová V, et al. Polymyalgia rheumatica and giant cell arteritis—an overview with a focus on important factors contributing to the severity of disease. In: Rovenský J, et al., editors. Polymyalgia rheumatica and giant cell arteritis. Bratislava: SAP; 2007. p. 7–32.
72. Leeb BF, Bird HA. A disease activity score for polymyalgia rheumatica. Ann Rheum Dis. 2004;63:1279–83.
73. Mohan N. Diagnosis of vasculitis. Best Pract Res Clin Rheumatol. 2001;15:203–23.
74. Langford CS. Management of systemic vasculitis. Best Pract Res Clin Rheumatol. 2001;15:281–97.
75. Paget SA. Diagnosis and management of giant cell arteritis. http://www.rheumatology.hss.edu/phys/specialReports/arteritis. Formát súboru asp.
76. Dasgupta B, Hassan N. Giant cell arteritis: recent advances and guidelines for management. Clin Exp Rheumatol. 2007;21(Suppl 44):S62–5.

77. Hoffman GS, Cid MC, Hellmann DB, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum. 2002;46:1309–48.
78. Lie MS, Smith SD, Galor A, et al. Antiplatelet and anticoagulant therapy in patients with giant cell arteritis. Arthritis Rheum. 2006;54:3306–9.
79. Mahr AD, Jover JA, Spiera RF, et al. Adjunctive methotrexate for treatment of giant cell arteritis. Arthritis Rheum. 2007;56:2789–97.
80. Catanoso MG, Macchioni P, Boiardi L, et al. Treatment of refractory polymyalgia rheumatica with etanercept: an open pilot study. Arthritis Rheum. 2007;57(8):1514–9.
81. Salvarini C, Cantini F, Niccoli L, et al. Treatment of refractory polymyalgia rheumatica with infliximab: a pilot study. J Rheumatol. 2003;30:760–3.
82. Both M, Aries PM, Muller-Hulsbeck S, et al. Balloon angioplasty of upper extremity in patients with extracranial giant cell arteritis. Ann Rheum Dis. 2006;65(9):1124–30.
83. Liu G, Shupak R, Chiu BK. Aortic dissection in giant cell arteritis. Semin Arthritis Rheum. 1995;25(3):160–71.