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HISTOPATHOLOGY OF GIANT CELL (TEMPORAL) ARTERITIS – CHANGES IN AORTA

ŠTVRTINA S.[1], ROVENSKÝ J.[2]

[1]Department of Pathology, Faculty of Medicine, Comenius University, Bratislava, Slovak Republic
[2]National Institute of Rheumatic Diseases (NURCH), Piešťany, Slovak Republic

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A b s t r a c t

Giant cell arteritis (GCA) is a systemic granulomatous vasculitis of unknown aetiology, which typically affects the branches of carotid artery (especially the temporal artery), but it can involve any medium-size or large artery, and then its diagnostics becomes much more difficult.

The aim of our study is to point up typical histopathological changes in the aorta of GCA patients.

In the study we discuss case reports of three patients in which the diagnosis of giant cell arteritis was established during autopsy. An 86-year-old man, who died of acute myocardial infarction, had aneurysms of the abdominal aorta and both iliac arteries. Death of an 84-year-old woman was caused by dissecting an aneurysm reaching from the ascending thoracic aorta to the abdominal aorta, ending at truncus coeliacus. The third patient, an 81-year-old man, had a dissecting aneurysm of the ascending aorta.

Typical histopathological changes in the aorta of patients with GCA include granulomatous inflammation, presence of giant cells – especially in media, atrophy of smooth muscles and destruction of elastic fibres, splitting and fragmentation of the lamina elastica interna, as well as deposition of calcium salts into the area of the lamina elastica interna, diffuse inflammation of the vessel wall, and ingrowth of capillaries (neovascularisation).

Giant cell arteritis involving the aorta can be a lethal disease and can be manifested in a dramatic way, by dissection or rupture of the aorta in the elderly. Early diagnostics of the disease, proper treatment, and life-long checks of patients with diagnosed GCA can prevent severe complications such as aortal aneurysm.

K e y w o r d s

Giant cell arteritis, Involvement of aorta, Histopathology, Aortic aneurysm

INTRODUCTION

Giant cell arteritis (GCA) is a systemic granulomatous vasculitis of unknown aetiology that, typically, involves the branches of carotid artery (especially of the temporal artery), but it can involve any medium-size or large artery, and then its diagnostics becomes much more difficult (*18*). Temporal arteritis is the most frequent form of giant cell arteritis. It is characterised by affecting the branches of carotid artery ("temporal" artery). The name "temporal" is quoted in inverted brackets because it expresses frequent but not necessary involvement of the temporal artery in this

disease. Temporal artery can be affected by the disease process also in other forms of vasculitides, as, e.g., in Wegener granulomatosis or microscopic polyarteritis. On the contrary, inflammation of the temporal artery is not necessarily manifested in all patients with giant cell arteritis (*4*).

Temporal arteritis (i.e. arteritis involving temporal artery) is not a lethal disease; the patients live the same average age as the other population. However, giant cell arteritis that involves medium-size and large arteries can be lethal and is often manifested in a dramatic way, via dissection or rupture of the aorta in the elderly, but also by myocardial infarction or emergency cerebral accidents (*9*). From the clinical point of view, temporal arteritis was for the first time described by *Hutchinso*n in 1890; the histopathological picture related to the clinical syndrome was outlined by *Horton* in 1932, but it was as late as in 1938 that *Jenning* recognised that blindness could be a grave complication of the disease (*7*). 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). In the clinical picture, two different sets of symptoms can be recognised - the first being temporal arteritis and the second polymyalgia rheumatica, described for the first time by William Bruce in 1888 (*10*). Today it is clear that GCA is a systemic condition with many severe, life-threatening cardiovascular complications. Its manifold and varying clinical picture and course of the disease are probably caused by the heterogeneity of both immune and inflammatory reaction in specific patients (*20*).

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

CASE REPORTS

CASE 1

An 86-year-old patient with a history of coronary artery disease and peptic ulcer, after anteroseptal myocardium infarction two years ago, was admitted to the hospital for a chest pain lasting for two hours. 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 due to the found 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 walls of the left ventricle and of papillary muscles of the mitral valve. When examining the abdominal aorta, two circular (ring-like) widenings of the lumen (aneurysms) were observed below the renal artery branches, and both iliac arteries were extended in a balloon-like way having 1.2 cm in diameter (*Fig. 1.*) One of the typical histopathological findings in GCA is a granuloma, or a granulomatous inflammation of the media, as we can see in *Fig. 2* in the abdominal aorta in our 86-year-old man (stained by hematoxylin-eosin - HE). In *Fig. 2* we can see an inflammatory infiltrate containing mostly histiocytes and plasmatic cells, not so many lymphocytes, and one giant multinucleate cell. In the area of the granuloma the structure of elastic fibres disappears. A typical multinucleate giant cell is in *Fig. 3*. All the layers of the vessel wall are involved, but most of them the media . The inner elastic membrane is split and fragmented, as is visible in *Fig. 4* in the same patient. *Fig. 4* shows also a calcium powder in the area of the lamina elastica interna. In another histological picture from the aorta of the same patient (*Fig.* 5) we can see typical multinucleate giant cells.

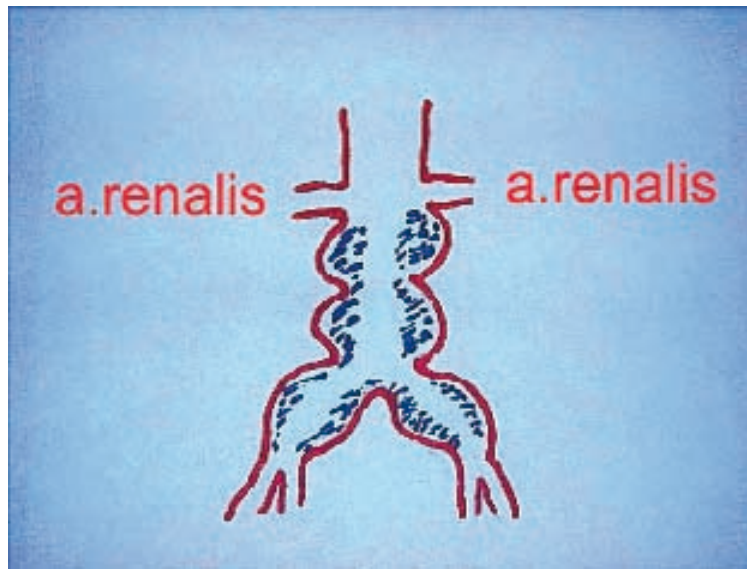

Fig. 1
Scheme of the aneurysms of abdominal aorta and common iliac arteries in an 86-year-old man

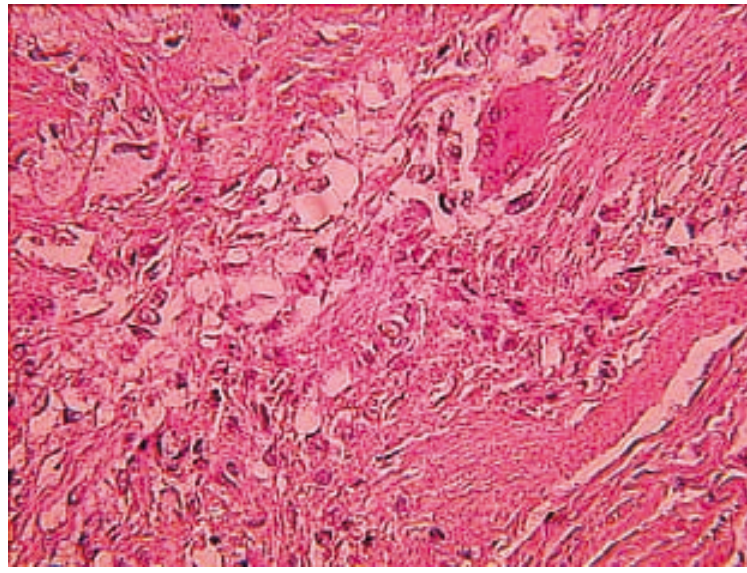

Fig. 2
Granulomatous inflammation of the media of abdominal aorta. Stained with HE – hematoxylin-eosin. Inflammatory infiltration formed mainly by histiocytes and plasmatic cells, less from lymphocytes, multinucleate giant cell

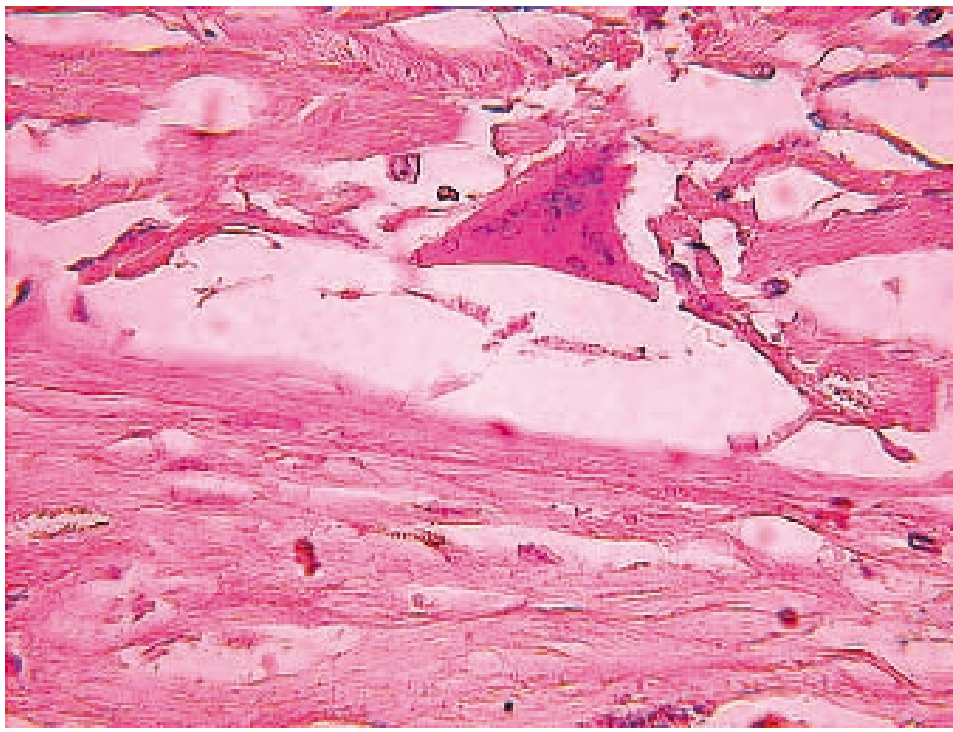

Fig. 3
Multinucleate giant cell. Stained with HE

CASE 2

An 84-year-old woman with a history of arterial hypertension and coronary artery disease, 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 accident. Her blood count showed severe anaemia (haemoglobin - 5.4 g/l) and leukocytosis (11 x 10^9/l). Cerebral CT did not show any fresh ischaemic or haemorrhagic lesion. The patient died after 6 hours of hospitalisation.

Macroscopic examination during her autopsy discovered a 3.5 cm long longitudinal tear at the posterior wall of the aorta 2 cm above the aortal valve; the tear formed a haematoma cavity between the adventitia and the media. The cavity continued to the abdominal aorta, and there, at the level of truncus coeliacus, 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 that continued to the descending thoracic and abdominal aorta (*Fig. 6*) was the cause of death of the patient. Histological investigation of the aortic wall revealed that the aneurysm had developed due to giant cell arteritis. In *Fig. 7* we can see a dissection in the media, where blue colour represents fibrin, which is a proof of blood flowing in the false lumen of the dissecting aneurysm (staining by phosphotungst haematoxylin). Panarteritis with a mixed inflammatory infiltrate (*Fig. 8*) was found in some parts of the aorta, whereas the other parts showed atrophy of smooth muscles of the media together with pronounced calcifications. Typical deposits of calcium salts in the aorta of our patient (*Fig. 9*) can be seen in the area of the lamina elastica interna (KOSSA staining); in the intima we can see an atherosclerotic plaque with calcium. *Fig. 10* shows calcium powder in the area of the lamina elastica interna in the same patient.

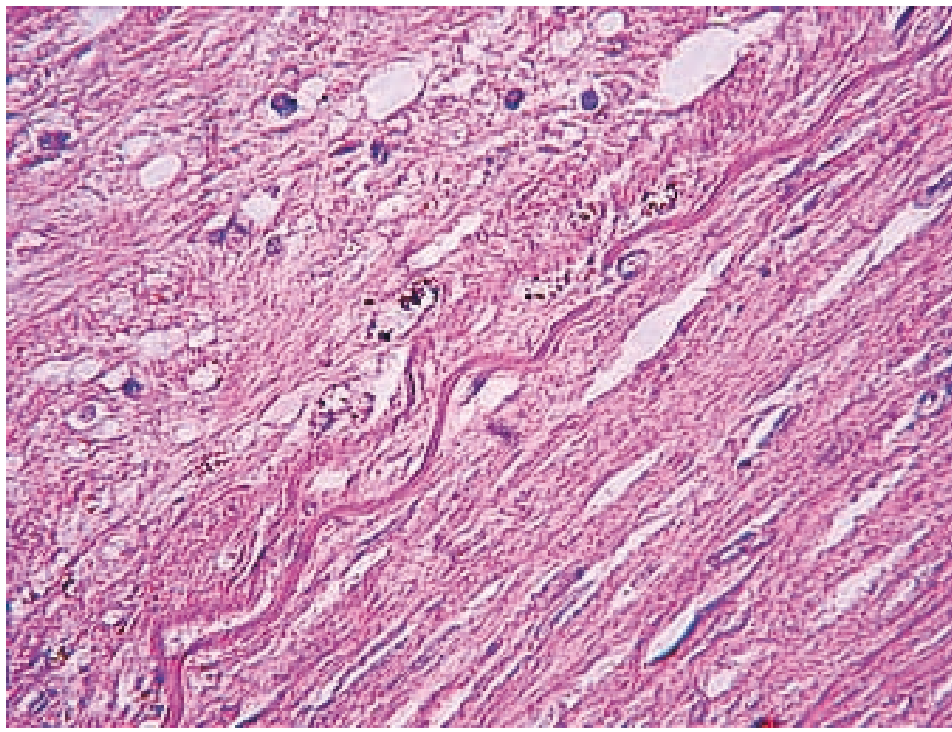

Fig. 4
Dissected and fragmented lamina elastica interna. Stained with HE

CASE 3

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

At the 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 created a sac between the adventitia and the media, 8 cm long, filled with dark red clots (*Fig. 11*). The cause of death in this patient was giant cell arteritis with a dissecting aneurysm of the ascending aorta. A fresh myocardial infarction supposed by the clinician was not proved by autopsy. The histological pictures of this 86-year-old patient's aorta showed a mixed inflammatory infiltrate (*Fig. 12*) and neovascularisation (*Fig. 13*) in the media of the aorta with inflammatory infiltration and destruction of the elastic fibres of the media.

DISCUSSION

Involvement of the aorta and its branches is observed in about 10–15 % of GCA patients. Affection of the aorta can be life-threatening due to the development of a dissecting aneurysm or rupture of the aorta (*7*). Giant cell arteritis is one of the

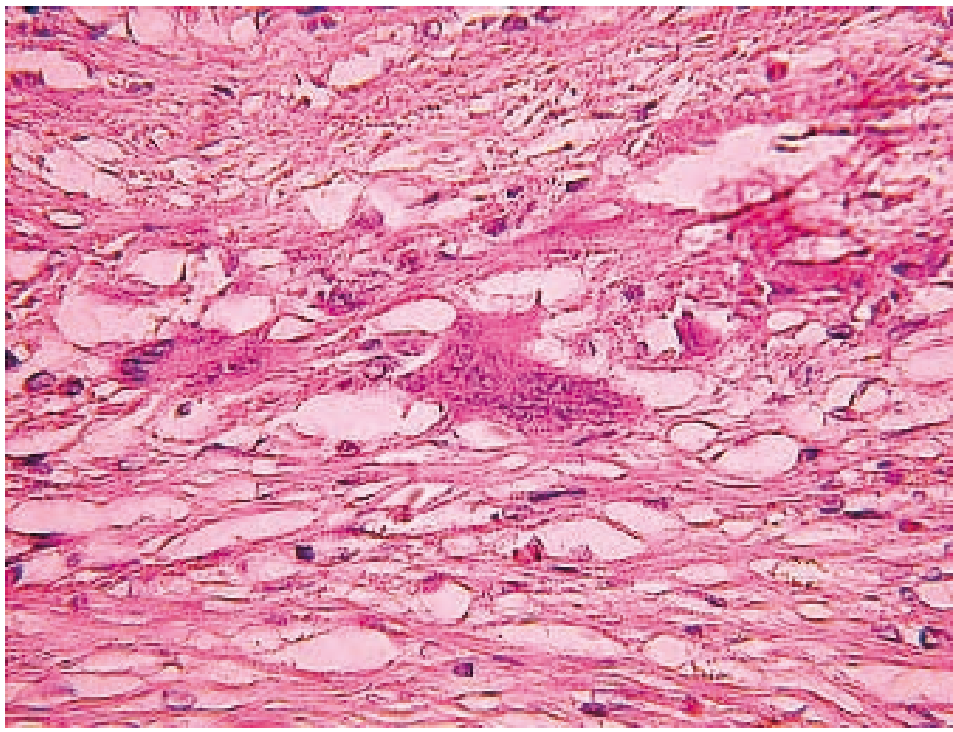

Fig. 5
Multinucleate giant cells. Stained with HE

most common vasculitides in the 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 – *16)*. In some patients a concomitant giant cell aortitis, aortic aneurysm, and aortic arch syndrome could be present (*15*).

The character of inflammatory damage in GCA is segmental. The intensity of the inflammatory response differs in different parts of the same vessel and in individual vessels, varying also in different stages of the disease (*17*). The classical picture of granulomatous inflammation with giant cells is observed in 50 % of the patients; the other half of the patients with positive histological findings show panarteritis with mixed inflammatory infiltrate, which is mainly of lymphomononuclear character with some neutrophils and eosinophils, but with no giant cells (*8*). Such panarteritis, developed into mixed inflammation consisting of polymorphonuclear leucocytes, lymphocytes, and plasmocytes is clear from *Fig. 8.* Two stages of inflammation are discerned in GCA (*11*). In atrophic arterial segments a focal, foreign-body, giant-cell

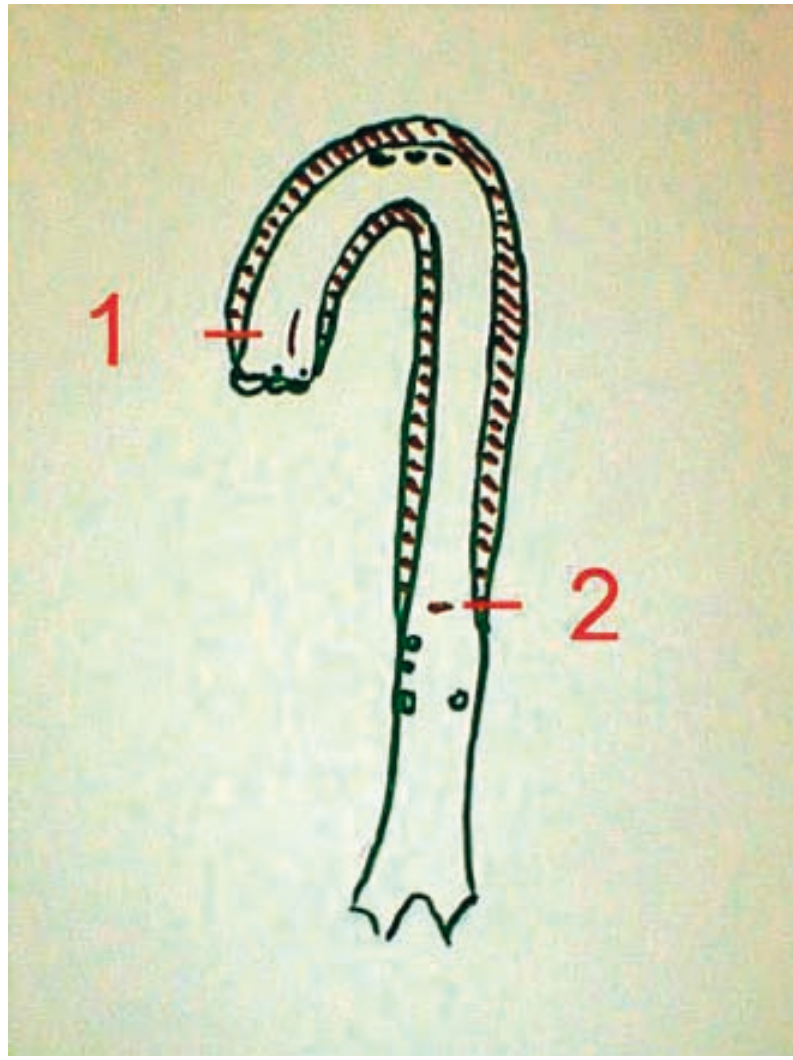

Fig. 6
Scheme of a dissecting aneurysm of the thoracic and abdominal aorta in an 84-year-old woman.
1 – beginning of dissection, 2 – end of dissection

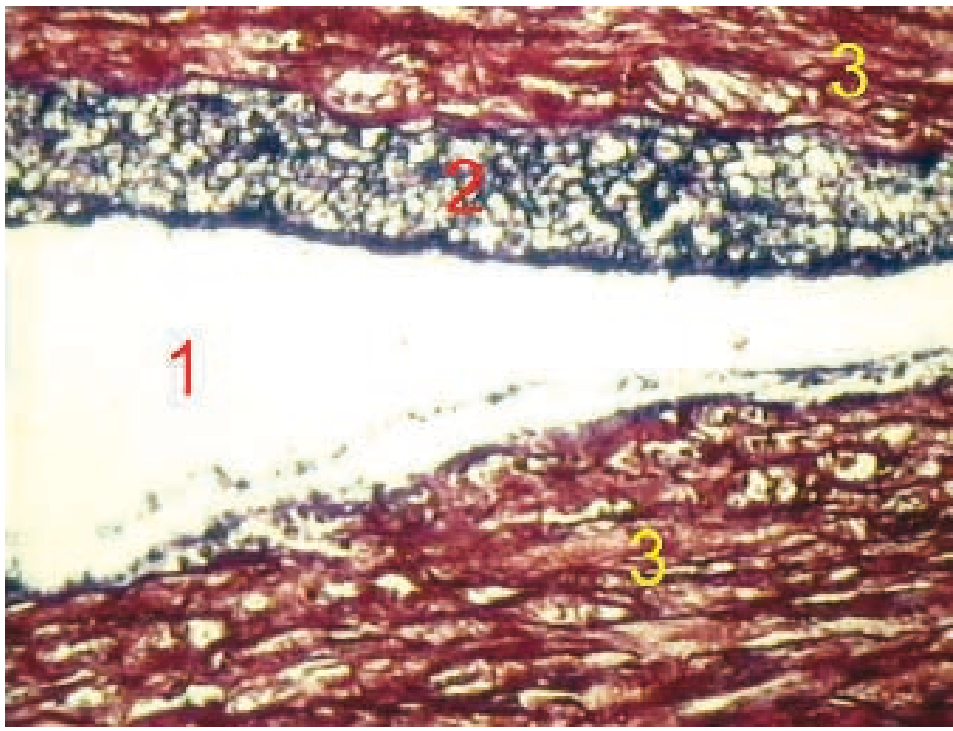

Fig. 7
Dissecting aneurysm of aorta in a patient with giant cell arteritis – dissection (1), fibrin (2), media (3). Stained with phosphotungst hematoxylin

reaction to the calcified internal elastic membrane was found, but in other biopsies a different picture with a diffuse macrophage attack on the media and intima with numerous and apparently macrophage-derived giant cells, which did not attack calcifications, was seen. Morphologically, the inflammatory process appears to be initiated by a foreign-body giant cell attack on the calcified internal elastic membrane in the 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 (*13*).

Giant cells obviously "attack" the inner elastic membrane and incorporate the calcified parts of the membrane. It seems that calcifications in the area of the lamina elastica interna and an atrophy of the media are inevitable prerequisites for the development of inflammatory response (*12*). Calcifications of the inner elastic membrane morphologically differ from calcifications developed at Monckeberg mediosclerosis, and from atherosclerotic calcifications (*14*). This is showed also in Figure 9 and

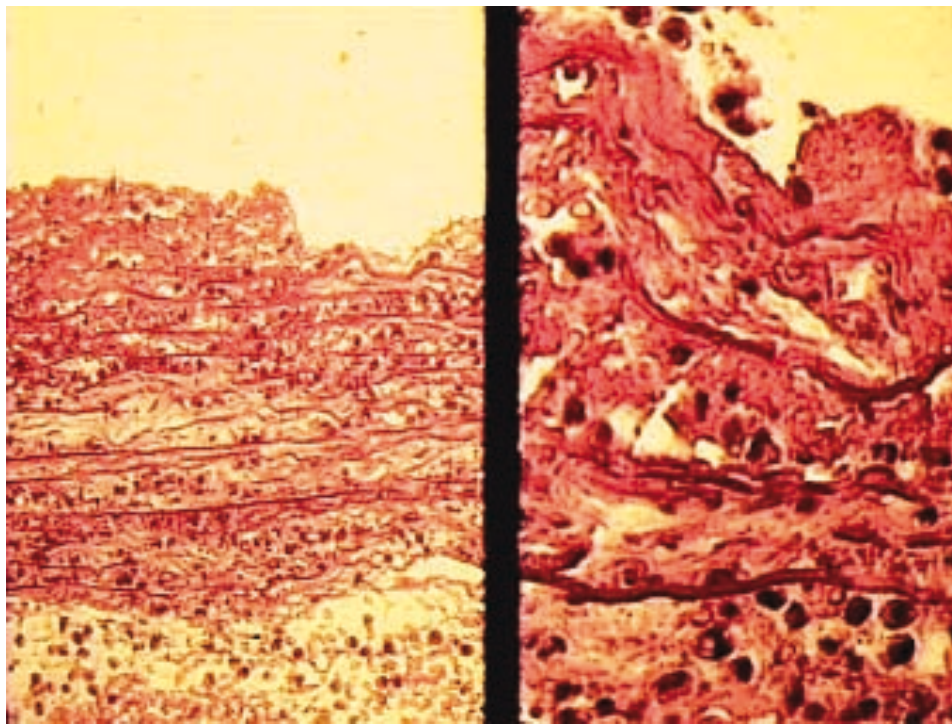

Fig. 8
Panarteritis – mixed inflammatory infiltrate. Stained with hematoxylin-eosin (HE)

this morphological difference will probably be, a reason why giant cells start gathering around the calcium in the lamina elastica interna. The analysis of vessel segments that are not affected by the inflammatory response showed a significantly greater atrophy of the smooth muscles of the media, and also calcifications in the area of the inner elastic membrane compared with the group of healthy volunteers. The involvement of arteries at the beginning of the disease can be caused by metabolic disorders in the arterial wall. This gradually leads to an 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 inner elastic membrane (*13*). With regard to the high age of patients with GCA, vasculitis can develop in the vascular wall already damaged by the atherosclerotic process, and the inflammatory response can be triggered by a so far unknown mechanism (*19*). Thus, in patients with GCA we can see both atherosclerotic and vasculitic changes, as is evident from *Figs 9* and *10*, where incorporation of calcium to the lamina elastica interna is a typical sign of

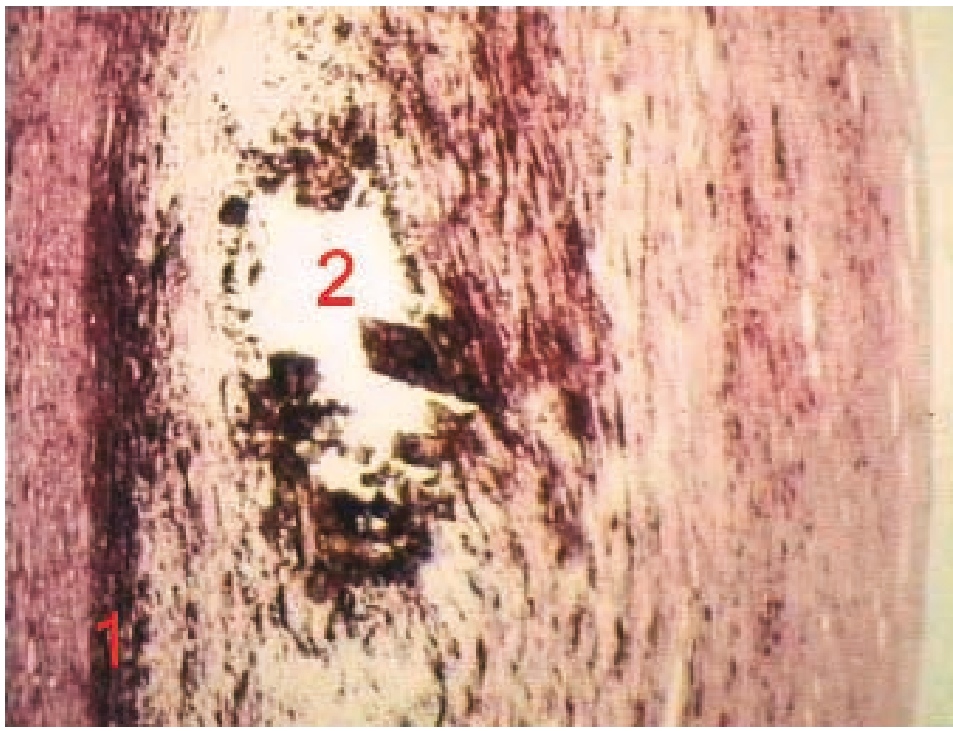

Fig. 9
Calcium deposits (1) in lamina elastica interna, sclerotic plaque with calcium in intima (2). Stained with Kossa and HE

vasculitis and an atherosclerotic plaque in the intima layer is a characteristic sign of atherosclerosis.

T lymphocytes 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 the production of proinflammatory cytokines. Macrophages in the media specialise in oxidative damage with lipid peroxidation, attacking smooth muscle cells and the 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 the fragmentation of the lamina elastica interna, the intimal layer becomes accessible to migratory myofibroblasts that later cause hyperplasia of the intima and occlusion of the vessel lumen (*21*). The 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

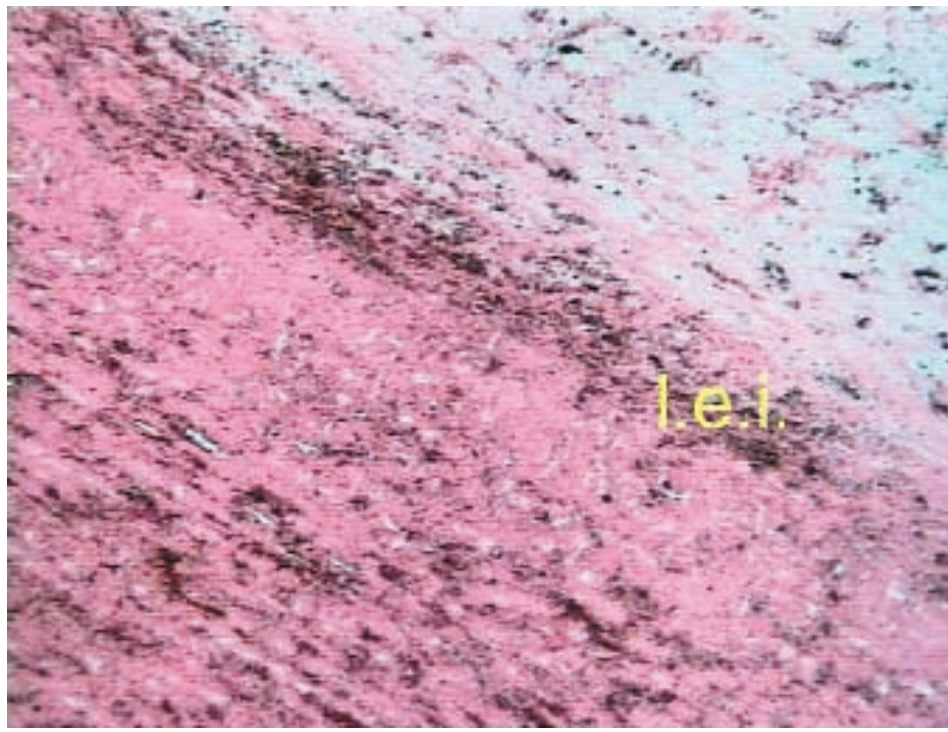

Fig. 10
Typical calcium powder in lamina elastica interna (l.e.i.). Stained with Kossa and HE

the intima (*6*). Neoangiogenesis was also present in the aorta of our 86-year-old patient (*Fig. 13*). .

Diagnosis of GCA is made through the characteristic histological finding, revealed at biopsy of the temporal artery, or from the material taken during surgery (*1*). Because the involvement of the vessels is segmental, meaning that biopsy may happen not to hit the right spot, bioptic examination of several cuts is recommended: the sections should be taken from a 5–8 cm big area of the temporal artery (*5*), the minimum being a 2–3 cm big spot. If the selected area of the artery gives a negative result in the biopsy, i.e. no arteritis can be proved, but there is still clinical suspicion of GCA, an examination of the temporal artery on the other side is recommended (*8*). Biopsy should be carried out before the therapy is started, since corticoid treatment decreases the value of bioptic examination (*8*). 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 the cases; however, a biopsy carried out a week after full treatment with corticoids is only positive in 20 % of patients (*10*).

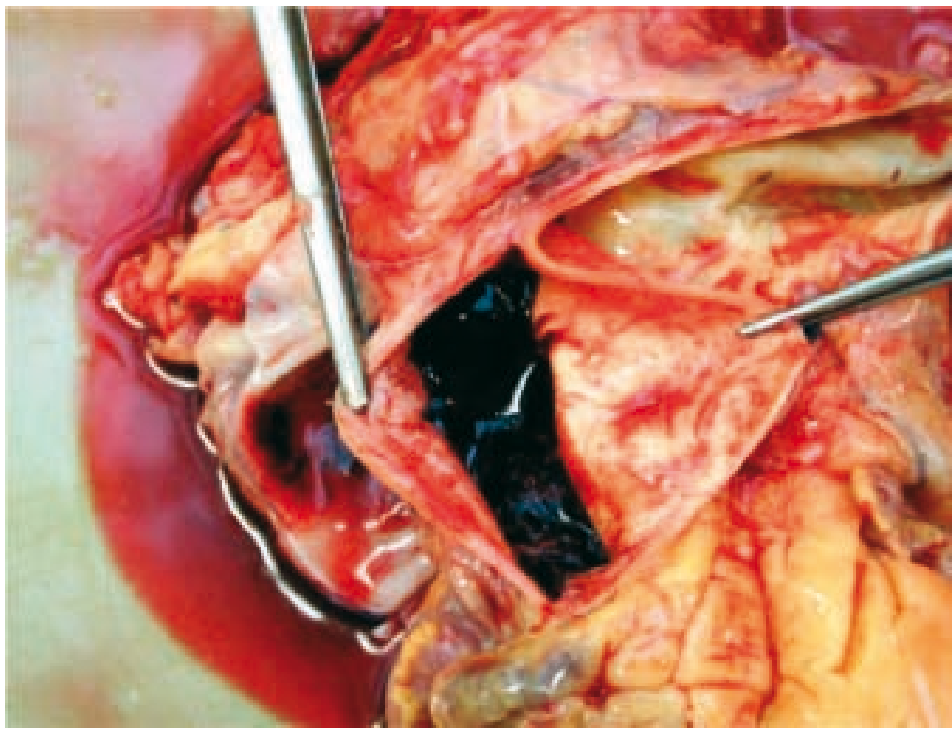

Fig. 11
Macroscopic photograph of the aortic arch – dissection of the aortic wall with blood coagulum

The survival of patients is not significantly shortened by the presence of giant cell arteritis (*3*), under the condition that the disease is early enough and properly treated. *Säve-Söderbergh et al.,* (*17*) describe the following causes of death in 9 GCA patients – two patients died of myocardial infarction, two of dissecting aneurysm, and five of sudden cerebral accident. None of the described patients was administered adequate corticoid therapy. *Lie* (*9*) reports 18 patients with extracranial GCA, with the following causes of death: rupture of aortal aneurysm in 6 patients, dissection of aorta in 6 patients, cerebral infarction in 3 patients, and myocardial infarction in 3 patients.

Since large arterial involvement in GCA can have fatal consequences, in all patients it is recommended to look for changes in these arteries in a focused way. Blood pressure should be measured in both upper extremities. Methods that enable estimation of the extent of arterial system affliction include ultrasound and angiographic examination. GCA significantly increases the risk of development of aortal aneurysm, which often presents a late complication of the disease that may cause death of patients. That is why it is necessary to actively seek for aneurysms in all

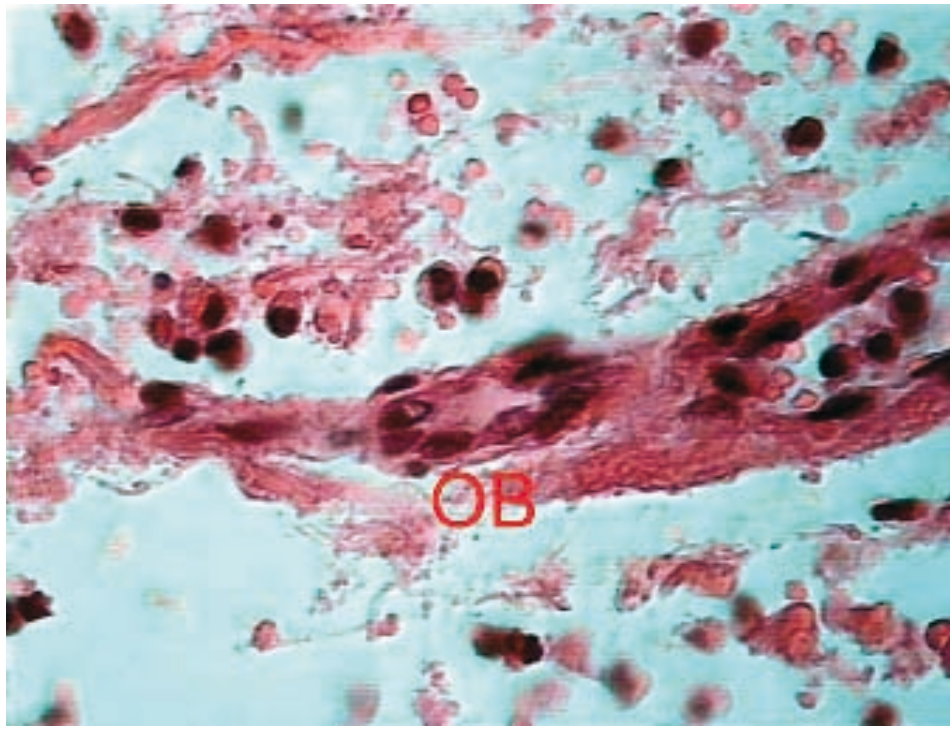

Fig. 12
Aortic wall - mixed inflammatory infiltrate, histiocytes and giant cell (OB) in adventitia.
Stained with HE

GCA patients – make regular duplex ultrasonography examinations, and also CT or MR examinations, if possible. Patients with diagnosed GCA should be carefully and properly treated, since in most of the patients in which aortal dissection developed the treatment was not adequate.

CONCLUSION

Giant cell arteritis involving the aorta can be a lethal disease and is often manifested in a dramatic way in the elderly: by dissection or rupture of the aorta. Early diagnostics, proper treatment, and life-long checks of patients in whom GCA was diagnosed can prevent the development of severe complications such as aortal aneurysm.

Typical histopathological changes in GCA include granulomatous inflammation, the presence of giant cells – especially in the media, atrophy of smooth muscles, and destruction of elastic fibres, splitting and fragmentation of the lamina elastica interna, as well as deposition of calcium salts into the area of the lamina elastica

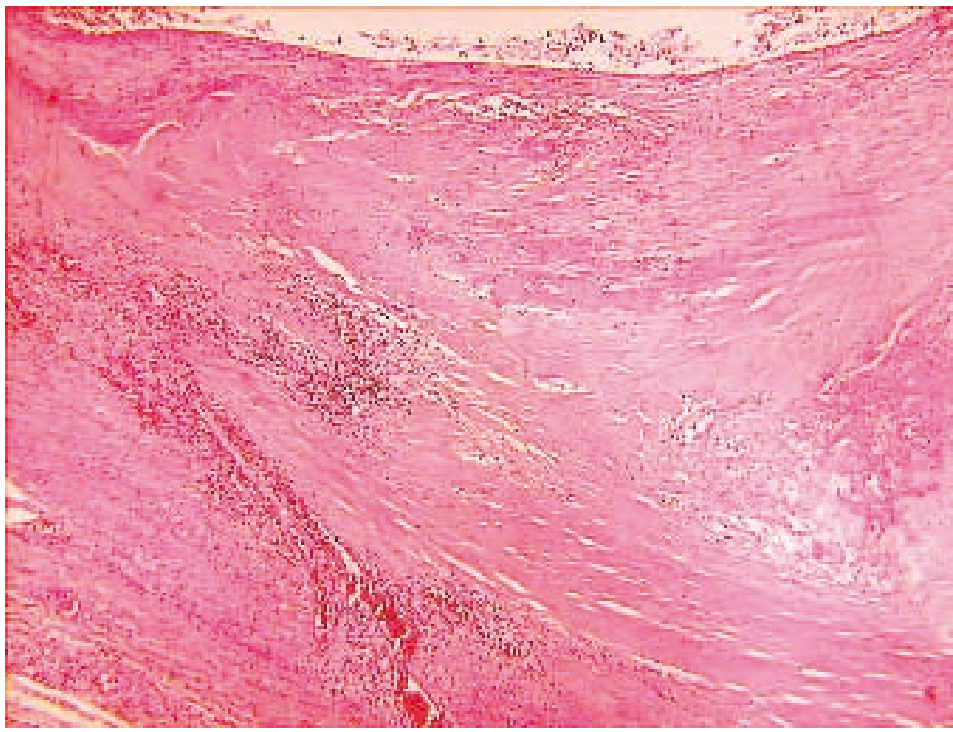

Fig. 13
Neovascularisation in the media of aorta

interna, diffuse inflammation of the vessel wall, and ingrowth of capillaries (neovascularisation).

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