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Polymyalgia Rheumatica and Giant Cell Arteritis

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Preface

In the present monograph, we offer current insights into polymyalgia rheumatica and giant cell arthritis. 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 arthritis, has serious consequences as well. Late diagnosis of giant cell arthritis 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 diagnosis, clinical course and treatment of rheumatic diseases in 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. The monograph is a result of cooperation among five institutions; the National Institute of Rheumatic Diseases in Piestany, Slovakia; Clinical Pharmacology Unit, Chapel Allerton Hospital Leeds, United Kingdom, the Department of Rheumatology in Stockerau, Austria; the Medical School of Comenius University in Bratislava and the Institute of Experimental Endocrinology in Bratislava, Slovakia. It is my great pleasure to appreciate the Slovak Research and Development Agency (APVV) for its financial support of polymyalgia rheumatica and giant cell arthritis research (this work was supported by Science and Technology Assistance Agency under the contract. No APVT-21-032304).

On behalf of all authors, Prof. MUDr. Jozef Rovenský, DSc. FRCP

Polymyalgia Rheumatica and Giant Cell Arteritis – an overview with a focus on important factors contributing to the severity of the disease

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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 under-recognised. 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 development of PMR and GCA also in 4th and 5th decade. Moreover, also juvenile temporary arteritis and GCA has 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). Whilst 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 as well as GCA are accompanied by a number of non-specific symptoms, such as lethargy, fatigue, fever, loss of appetite and weight, and overall weakness. William Bruce described PMR symptoms for the first time in 1888 (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 thought to be primarily age-related, despite the fact that 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, lead to a tremendous improvement of the affected patients in general.

GCA is a primary systemic vasculitis mainly affecting large vessels of 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 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 is 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, tender, with palpable nodules along the artery and reduced or even absent pulsation (Fig. 1). In any case of supected temporal arteritis an ultrasound examination 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). Although biopsy should be considered very important, the required treatment, however, should not be postponed due to biopsy procedure. GCA of the temporal artery does not necessarily constitute the only manifestation of the disease. Therefore, a negative biopsy of the temporal artery does not exclude GCA (12) Nevertheless, in doubtful cases a biopsy of the temporal artery may contribute to an ultimate clarification. However, it has to be pointed out that GCA of the temporal artery not necessarily constitutes the only manifestation of the disease.

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. It 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). 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).

1.4 Laboratory findings

Laboratory changes are generally non-specific, 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, despite the fact that PMR may also exist without elevated acute phase reactants (21). Martinez-Taboada et al. (22) suggested a limit of 30 mm/hour, 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 leucocytes count can be found within the normal range. Positive rheumatoid factors concentrations or elevated antinuclear antibodies are to be seen occasionally. Muscle enzymes, such as creatine-kinase 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 intralobal 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 glucocorti-

coid 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 CD8+ 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 that to prove PMR (27, 28).

1.5 Differential diagnosis

The more unspecific the patient's symptoms are the more important become considerations 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 titres 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 typically are 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 after a period of time. Polymyalgic syndromes may also of paraneoplastic nature (30). The recommendation to investigate PMR patients thoroughly the younger they are and the less impressive their response to corticoids is, particularly if they are male can be given as a rough rule of thumb.

PMR/GCA like symptoms may also occur with hypothyroidism, with chronic septic disorders and inflammatory myopathic disorder. Bilateral shoulder joint capsulitis can be quite easily distinguished from PMR on the basis of 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 hallmarks 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.

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 has to be measured at both upper extremities, palpation for peripheral pulsation and auscultation for murmurs along large extremity vessels is 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. Negative biopsy findings do to exclude the GCA diagnosis in case of remaining clinically suspected disease. 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 (Fig. 23, 24) 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 (31). Temporal arteritis may be found also in case of other vasculitis disorders, such as Wegner's granulomatosis or microscopic polyarteritis. On the other hand, inflammation of the temporal artery not necessarily occurs in all GCA patients (32).

1.6 Aetiopathogenesis

The aetiology and pathogenesis of PMR and GCA are not elucidated yet. However, considerations in this respect are focussed on environmental factors-particularly infections with Chlamydia, Mycoplasma, Parainfluenza-virus or Parvovirus B19 – and genetic ones. An association with the HLA system as well as a number of 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 CD8+ T-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 a number of neuroendocrine changes relating to natural aging.

1

Concentrations of several hormones are known to undergo changes in elderly e.g. decrease in adrenal androgen levels such as of dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS) and androstenedione (ASD). Reduction of adrenal androgen levels has been inversely correlated with concentrations of pro-inflammatory cytokines such as TNF and IL-6 (33). Thus, the natural decrease of the adrenal androgens associated with an increase in the concentrations of pro-inflammatory 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 (34).

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 (35, 36). An intricate feedback system probably maintains cortisol levels within the normal range. Because of the ongoing inflammation however cortisol secretion remains insufficient (36). 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 (37). 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 (35). 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 be similar to 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. (38) 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 B19 infections. Second seasonal changes in the immune system making human organism more responsive to the development of various diseases including PMR.

As in rheumatoid arthritis the HLA DRB1*04 and DRB1*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 (39). Antigen recognition by T-cells in the adventitia with subsequent production of interferon-γ 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-α, 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 (39).

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 has significantly decreased due to the improvement in diagnosing GCA. Nevertheless, still up to 15% of the patients develop this complication. Ischemia of the anterior optic nerve is mainly reported as a result 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 over night in form of blurred vision, diplopia, light scotomas, visual field narrowing or even transient or irreversible blindness (reported in less than 10% of patients) have 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 have been reported. 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 haemorrhage (Fig. 2a, b). 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 (Fig. 3), abducens or the trochlear nerves is quite rare, and has been reported only in 2% of GCA patients. Early recognition of visual disturbances alerting potential vision impairment (temporary scotomata, phosphorescent phenomena etc.) can contribute to prevent vision loss (12, 40, 41, 42, 43, 44, 45).

Some improvement in diagnostics may be expected thanks to the use of imaging techniques, such as coloured 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 app. 20 to 30% of the patients, caused by vasculitis of nutrition vessels. Clinical manifestations may comprise deafness, hemiparesis, depression, confusion and peripheral neuropathy (in app. 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, have 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 (46).

Aside pain in the temporal or/and 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, in form of strokes or transitory ischemic attacks (TIAs) is only rarely observed in GCA patients; according to Nesher in 166 biopsy-proven GCA patients 6% experienced a TIA and 3% a stroke (46). 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 (47), as GCA probably accelerates atherosclerotic changes (48).

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 form of monolateral or bilateral deafness, vertigo or tinnitus with a beneficial effect of glucocorticoid treatment.

Chronobiology of Polymyalgia Rheumatica and Giant Cell Arteritis

8

Howard Bird

8.1 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.

8.2 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 0500 hours, 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 neuro-endocrine 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).

8.3 Mechanisms of Variation

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 hours 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 neuro-hormones, particularly cortisol and MLT. In normal subjects, MLT peaks at about 0300 hours whereas cortisol peaks at 0400 hours. 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 TNFα 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 TNFα concentrations were observed in RA in patients from Estonia and Italy at 0400 hours 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.

8.4 Diurnal Variation in Polymyalgia Rheumatica/Giant Cell Arteritis

The presence of severe early morning stiffness figures prominently in several diagnostic criteria sets (10, 11, 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, TNFα, IL-6, IL-1 receptor antagonist levels as well as 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 TNFα 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.

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 (15), a winter peak of incidence was once again identified, perhaps suggesting an infective aetiology at that time of year.

8.5 Implications 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 2002 (16). This considered not only pharmacological variation between the different steroid analogues available commercially (17) (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

Fig. 8
Multinucleated giant cell. Stained with HE.

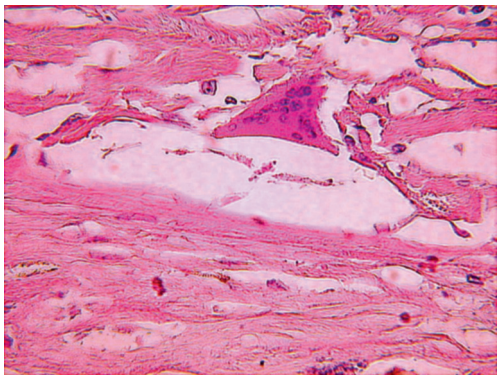


Fig. 9
Dissected and fragmentated lamina elastica interna. Stained with HE.

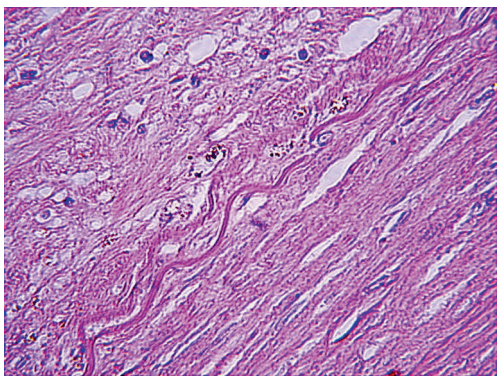
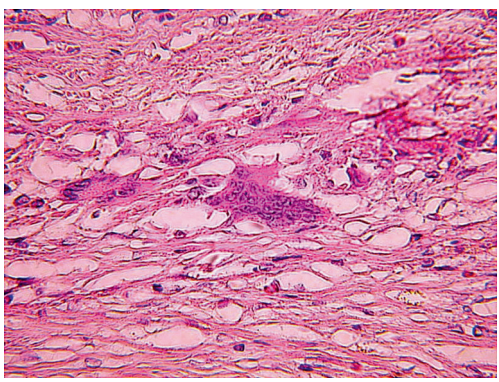


Fig. 10
Multinucleated giant cells. Stained with HE.



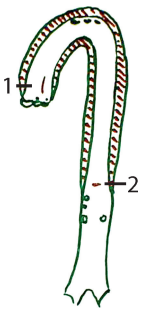


Fig. 11
Scheme of dissecting aneurysm of the thoracic and abdominal aorta in an 84 year old woman. 1 – beginning of the dissection, 2 – end of the dissection.

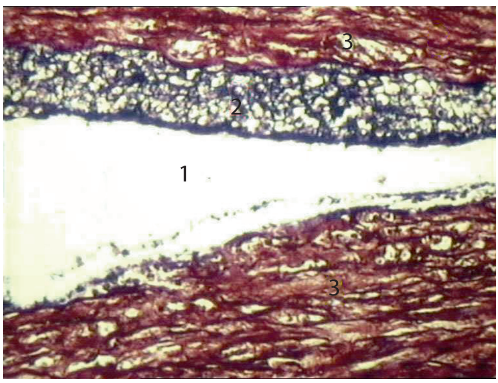


Fig. 12
Dissecting aneurysm of aorta in a patient with giant cells arteritis – dissection (1), fibrin (2), and media (3). Stained with fosfowolfram hematoxylin.

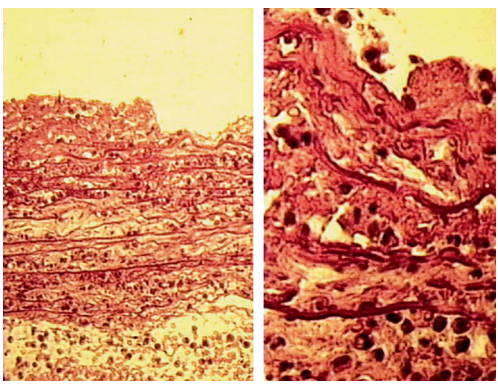


Fig. 13 Panarteritis – mixed inflammatory infiltrate. Stained with hematoxylin – eosin (HE).

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