The pathogenesis of giant cell arteritis: Morphological aspects

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These studies were supported by grants from the Göteborg Medical Society, the Swedish Heart-Lung Foundation, the Swedish Rheumatism Association, Rune och Ulla Amlöfs Stiftelse and Syskonen Holmströms Donationsfond.

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Clin Exp Rheumatol 2000: 18 (Suppl. 20): S18-S21.

Key words: Giant cell arteritis, light microscopy, electron microscopy, morphometry, immunocytochemistry.

ABSTRACT

The light-microscopic, electron-microscopic and immunocytochemical characteristics of giant cell arteritis (GCA) have been investigated in a number of studies on temporal arteries. Arterial atrophy and calcification of the internal elastic membrane appear to be prerequisites for the evolution of the inflammatory process. Foreign body giant cells form close to calcifications, apparently without connection with other inflammatory cells and probably by the fusion of modified vascular smooth muscle cells. The foreign body giant cells attack the calcifications. Lymphocytes accumulate around them and may be found in pockets in their cell surface.

This focal reaction is found in atrophic, calcified arterial segments in a minority of inflamed temporal artery biopsies. More commonly seen is a diffuse mononuclear attack of the vessel wall in atrophic as well as non-atrophic segments which leads to severe arterial dilatation. Langhans giant cells form by the fusion of macrophages in the diffuse inflammatory infiltrate.

The fact that the diffusely inflamed arteries are markedly widened compared to the focally inflamed vessels suggests that the inflammatory process starts as a focal foreign body giant cell reaction directed at calcifications which in turn initiates a more diffuse and widespread inflammation.

Introduction

Giant cell arteritis is a chronic form of vasculitis which predominantly affects women over 50 years of age. Its etiology and pathogenesis are incompletely understood. Genetic factors are of relevance; the disease is more common in Caucasians and in patients expressing the histocompatibility antigen HLA-DR4 (1). Immunological analysis of the inflammatory infiltrate in the vessel wall indicates the local activation of T-lymphocytes (2), which supports the theory that cell-mediated immunity is involved in GCA. When studying V-beta families of the T-cell infiltrate with flow cytometry, Schaufelberger *et al*. found that the infiltrating lymphocytes are polyclonal (3). On the other hand, Weyand *et al*. (4) demonstrated the identical clonal expansion of a small proportion of the T-lymphocytes in separate segments of the same artery, which indicates antigen stimulation. A correlation between various infections and the onset of GCA has been reported; it has been speculated that infectious disorders might trigger the inflammatory process (5). Zoster-varicella infection may induce granulomatous angiitis. However, immunocytochemistry or PCR did not reveal this type of virus in inflamed temporal arterial tissue from 10 GCA patients (6).

Atrophy and calcification of the temporal artery

A previous morphometric study showed that asymmetric atrophy of the temporal artery media and an accompanying focal calcification of the internal elastic membrane (IEM) are significantly more pronounced in non-inflamed arterial segments in polymyalgia rheumatica than in controls (7). This type of atrophy should not be confused with post-inflammatory scarring. The atrophic arteries display an asymmetric reduction of the media, which may be lost in part of the circumference but there is no fibroblastic or microvascular proliferation. Moreover, morphometry showed that the atrophic, calcified arterial segments had a significantly smaller outer diameter than the inflamed vessels (7). This indicates that the atrophy and calcification are not the result of scarring after arteritic inflammation since arteries which are dilated due to a weakening of their wall do not regain their original circumference. Finally, the fact that the same type of calcification and media asymmetry may be seen in normal arterial aging, although to a lesser extent, speaks in favour of a primary atrophy which is not the result of previous inflammation.

The morphology of the inflammatory process

According to a light-microscopic examination of semi-thin plastic sections, foreign-body giant cells form focally around the calcifications in atrophic segments of the temporal artery. Serial sectioning revealed giant cells in segments which were devoid of other inflammatory cells (7). The immuno-phenotype and ultrastructure of the foreign-body giant cells and the polygonal cells with which they fuse indicate that they might be formed by the fusion of modified arterial smooth muscle cells (7, 8). The induction of this fusion, which always takes place close to calcifications, needs further clarification.

Mononuclear cells accumulate around the foreign-body giant cells; some lymphocytes may even be found in shallow pockets in the giant cell surface. It remains to be shown whether the foreign-body giant cells present antigen to these surrounding lymphocytes, thereby initiating T-cell activation. An association between the foreign-body giant cell reaction and T-cell activation has previously been suggested around silicone gel breast implants (9).

The fact that the foreign-body giant cell granuloma, in its pure form, is only found in a minority of temporal artery biopsies may be due to its focality but may also indicate that it is a short-lasting reaction which is soon replaced by a diffuse mononuclear cell invasion. In most biopsies the mononuclear infiltration is more widespread, involving the whole circumference of the artery in atrophic as well as non-atrophic arterial segments. Langhans giant cells form in the diffuse inflammatory infiltrate by the fusion of macrophages (7, 8).

Consequently, according to the light-microscopic findings the site of ignition for the inflammatory reaction in GCA appears to be the foreign-body giant cell reaction to calcified IEM. The mononuclear inflammation subsequently becomes more diffuse and spreads also into non-atrophic arterial segments (7, 8). This order of the inflammatory events is supported by the fact that the diffusely inflamed arteries were significantly wider than those which displayed the focal foreign-body giant cell reaction (7). Once widened by the weakening of their wall, arteries do never regain their original outer diameter.

Giant cell aortitis

Morphological and morphometric analyses thus indicate that atrophy and calcification are a prerequisite for the initiation of the inflammatory process in temporal arteries. Analogously, the aortic inflammatory reaction in GCA is related to smooth muscle atrophy and calcification. Petursdottir *et al*. (10) showed laminar smooth muscle atrophy and calcification in the aortic media from patients with GCA. The inflammatory reaction and the breakdown of elastic lamellae was confined to the borders of such atrophic lesions. The findings support the contention that atrophy and calcification preceed the inflammatory reaction which is, in fact, primarily directed at calcified tissue. Moreover, the coupling to arterial atrophy and calcification may explain why GCA is a disorder of elderly people.

The origin of the inflammatory infiltrate

The distribution of inflammatory cells in the arterial wall indicates that the majority of the invading cells are recruited from microvessels in the adventitia, whereas a minority seem to emanate from the lumen of the inflamed artery (11, 12). One evidence of cellular migration from the adventitia into the vessel wall is the crowding of inflammatory cells at the outer margin of the media, as would be expected if cells were migrating from the loose adventital connective tissue into the tighter smooth muscle layer. Within the intima, the inflammatory cells accumulate peripherally around the IEM (11). The current observations thus suggest that the inflammatory cells are mainly recruited from the adventitial microvessels, whereas the target of the inflammatory reaction is situated in the peripheral intima. CD4+ T cells dominated the inflammatory infiltrate, which is in accordance with other investigations (11, 13).

Estrogen metabolism in GCA

Could the fact that GCA is far more common among women than among men and is rarely seen before the age of 50 be related to differences in sex hormone metabolism ? The estrogen production of pre-menopausal women is cyclic, with a higher secretion rate than in men. Moreover, menopause implies a major change in estrogen metabolism. A recent epidemiologic study indicates that former pregnancies may be a protective factor against GCA (14), which supports the contention that GCA may be related to estrogen metabolism. Theoretically, it could influence the pathogenesis of GCA in several ways. Functioning estrogen receptors have been detected in cultured human vascular smooth muscle cells, indicating that estrogen may be involved in vessel wall metabolism. Moreover, a number of studies suggest that estrogen plays an important role in immunology. In a recent immunocytochemical study we found that the inflamed arteries in GCA expressed distinct cytoplasmic immunoreactivity to estrogen receptor alpha (ERα) in activated mononuclear inflammatory cells and in giant cells (15). Furthermore, biopsies from GCA patients and from non-GCA controls displayed cytoplasmic immunopositivity in smooth muscle cells. Western blot analysis revealed a band corresponding to the wild type ERα in inflamed arteries and in controls and RT-PCR analysis revealed a strong band corresponding to approximately 670 bp, as expected (15). These findings justify further studies regarding the roles of estrogen metabolism in vascular aging and GCA.

Hypothesis

Based on our morphological observations we have formed the following hypothesis regarding the evolution of the inflammatory reaction in GCA; this hypothesis is also illustrated in Figure 1.

Arterial atrophy and calcification are prerequisites. Foreign-body giant cells form close to elastin-related calcifications without apparent connection with other inflammatory cells, probably by the fusion of modified smooth muscle cells. The foreign-body giant cells attack calcifications. Lymphocytes are attracted to the giant cells and may be found in pockets at their periphery. It remains to be shown if the giant cells present antigens, thereby initiating the subsequent diffuse

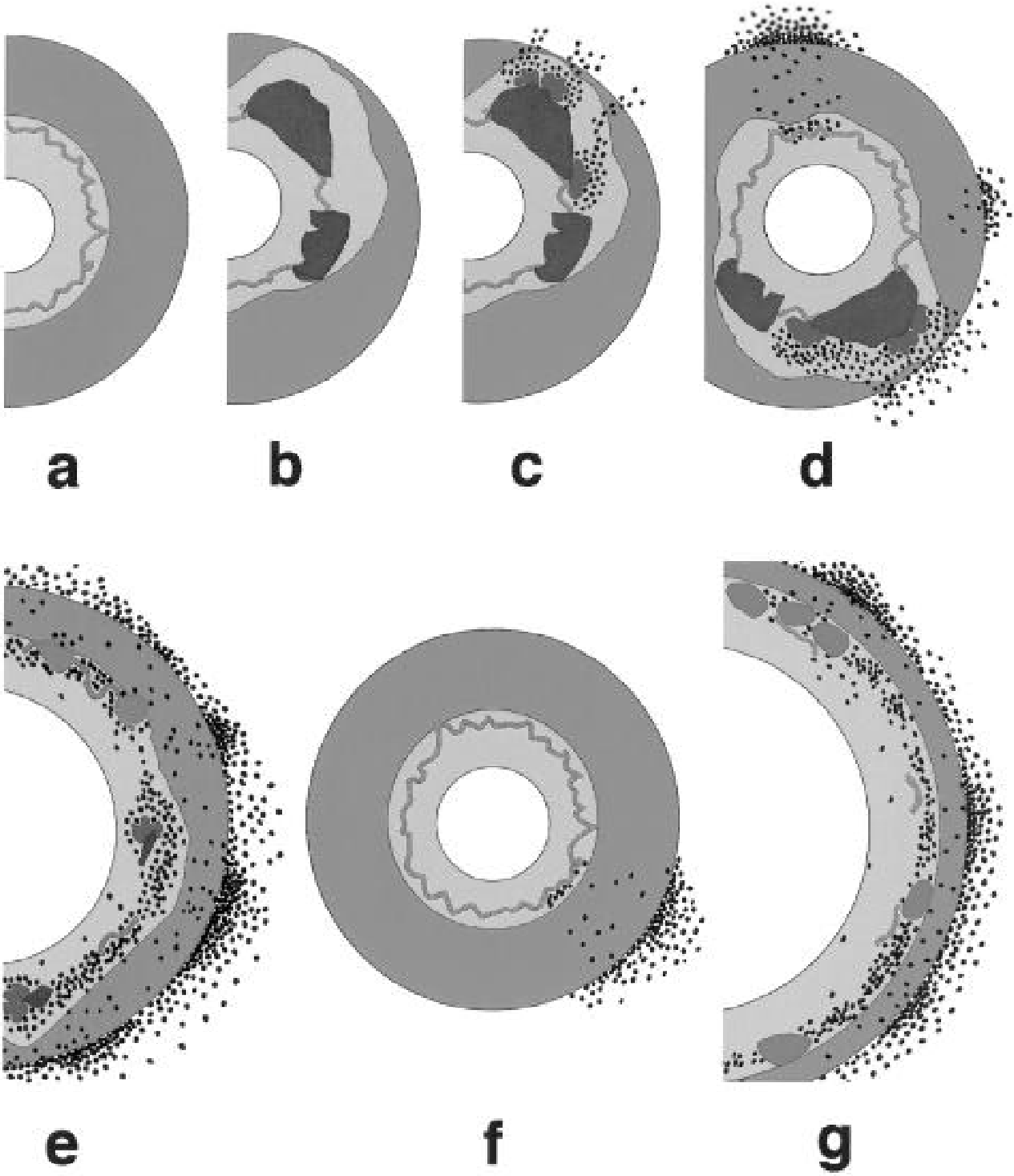

Fig. 1. Suggested morphological evolution of the inflammatory reaction in GCA. (**a**) Normal artery media: brown; intima: yellow; internal elastic membrane: blue. (**b**) Asymmetric atrophy of the media and focal calcification (dark brown) of the internal elastic membrane are more pronounced in temporal arteries in GCA. (**c**) The starting point of the inflammatory reaction is a focal foreign-body giant cell attack on the calcifications. The foreign-body giant cells (red) attract mononuclear cells (dark points). Lymphocytes may be seen in pockets in the giant cell surface. (**d**) The inflammatory reaction then spreads to other parts of the atrophic arterial segment. The inflammatory cells are mainly recruited from the adventitia and migrate through the media, causing cell crowding at its outer border. (**e**) The severely inflamed atrophic segment dilates due to destruction of the media and internal elastic membrane. The foreign-body giant cell reaction is now less pronounced. Langhans giant cells (green) form by the fusion of macrophages. (**f**) The inflammation also spreads to non-atrophic, non-calcified segments. Mononuclear cells (dark points) are recruited mainly from the adventitia and invade the arterial wall, causing crowding outside the media. (**g**) The inflammation also increases in non-atrophic segments, causing dilatation due to destruction of the media and internal elastic membrane. Mononuclear cells accumulate in the peripheral intima. Langhans giant cells (green) form by the fusion of macrophages.

mononuclear attack which leads to severe destruction and dilatation of the arterial wall. The diffuse inflammation also spreads into non-atrophic segments. In the diffuse phase, Langhans giant cells form by the fusion of macrophages.

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