Case Report

Takayasu Arteritis and Atherosclerosis: Illustrating the Consequences of Endothelial Damage

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ABSTRACT. The excess of cardiovascular morbidity associated with chronic vasculitic disease has become a focus of considerable research, particularly regarding the link between endothelial damage and the development of atherosclerosis. We describe a case of Takayasu arteritis treated sub-optimally by today's standards, giving rise to an 11 year history of progressive, stepwise decline associated with cerebrovascular events and leading to early death. Postmortem findings presented a picture of chronic atherosclerotic disease but in a distribution consistent with lesions of Takayasu arteritis. (J Rheumatol 2001;28:2752–3)

Key Indexing Terms:
TAKAYASU'S ARTERITIS ATHEROSCLEROSIS
VASCULITIS ENDOTHELIUM ENDOTHELIAL DYSFUNCTION

Diseases with a significant vasculitic component usually respond well to immunosuppressive therapy in the short term, but there is concern that in the long term persistent disease activity may bring about an increased morbidity and mortality due to cardiovascular disease. This is most dramatically illustrated in systemic lupus erythematosus (SLE), where cardiovascular mortality is well in excess of that resulting from corticosteroid therapy alone[1] and is well described in rheumatoid arthritis[2]. We describe a case of Takayasu arteritis receiving sub-optimal therapy by the standards of current treatment protocols. Persistent disease activity resulted in presentation with multiple cerebrovascular events over many years. Postmortem findings were of florid, accelerated atherosclerotic disease thought to be late lesions of Takayasu arteritis.

CASE REPORT

In April 1998 a 45-year-old man was transferred to the Queen Elizabeth Neurosciences Centre for investigation. He had a history of gradually deteriorating cognitive function and general self-neglect. Transfer was prompted by an acute deterioration with confusion, ataxic gait, and incontinence. He had smoked 10 cigarettes a day for many years and was taking bendrofluazide for long-standing hypertension and low dose aspirin.

His history dated from 1987, when he was admitted to a neurology unit with systemic malaise, profound ataxia, dysarthria and dysphagia, nystagmus and right sided spinothalamic sensory loss. A brain stem syndrome was diagnosed; however, investigation revealed only an elevated erythrocyte sedimentation rate (ESR). He improved spontaneously and was discharged, only to be readmitted 2 months later with an identical brain stem episode and an ESR of 120 mm/h. A weak pulse in one arm was noted, but no blood pressure deficit was found. On suspicion of an underlying vasculitis, oral prednisolone 60 mg daily was started, resulting in an improvement in symptoms accompanied by a falling ESR. He was lost to followup in 1990, by which time the ESR was normal and steroids had been withdrawn. In 1997 he was investigated by a local vascular surgeon after a number of presumed cerebrovascular events. Examination revealed poor upper limb pulses with unrecordable blood pressure in the right arm. An arch aortogram and subclavian angiogram showed occlusions of the left common carotid and both subclavian arteries. Because of their length and location the lesions were not amenable to angioplasty or stenting; he was not offered surgery and was again lost to followup.

Examination on admission to the Queen Elizabeth Neurosciences Centre revealed impalpable upper limb pulses, a right carotid bruit, and undetectable blood pressure in the arms. Cognitive function was poor; examination of the limbs revealed marked ataxia, brisk reflexes, and extensor plantar responses. Investigations revealed ESR 50 mm/h and C-reactive protein (CRP) 19 mg/l (normal < 5 mg/l). Echocardiogram was normal. Immunology, thrombophilia, and anticardiolipin investigations were negative. There was no evidence of infective central nervous disease, vitamin deficiency, or endocrine disease. Magnetic resonance imaging and computerized tomographic scans revealed multiple infarcts consistent with ischemic cerebrovascular disease; a diagnosis of multiple infarcts secondary to a recurrence of cerebral arteritis was made. General improvement occurred taking 60 mg prednisolone and he was discharged, only to be readmitted 2 months later with further cognitive decline. The patient was now unable to give a history, exhibiting marked psychomotor retardation and a fluctuant response to command. There were no new cardiovascular or focal neurological signs. Investigations showed mild normochromic, normocytic anemia, ESR 58 mm/h, and CRP 99 mg/l (normal < 5 mg/l). At this point he was referred to the Department of Rheumatology.

His angiogram films of 1997 were obtained; these confirmed the diagnosis of Takayasu arteritis as indicated by the combination of radiographic appearance, clinical signs, and raised inflammatory markers. It was agreed that his rapid deterioration in the presence of an inflammatory response justified a trial of intravenous pulse cyclophosphamide and methylprednisolone. However, a lack of clinical response to 3 pulses prompted withdrawal of aggressive therapy. Some weeks later sudden deterioration occurred, management was conservative, and the patient died.

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Post mortem findings. There was evidence of postinflammatory fibrosis affecting the main upper body arteries and coronary arteries. The common carotid arteries showed differing degrees of intimal fibromuscular proliferation and adventitial fibrosis. The left was completely occluded. Similar changes were seen in the coronary arteries (Figure 1). In any single section these presented a picture of atherosclerosis; however, the changes were uniform and affected long lengths of artery rather than forming discrete plaques in the typical manner of atheroma. The changes in the aorta were more focal, and definite atheromatous plaques were present. There was no evidence of arteritis related renal artery stenosis. A small artery in the vasa vasorum of the arch of the aorta showed changes typical of previous active vasculitis (Figure 2). In the brain there were multiple areas of cerebral softening secondary to ischemic infarcts.

DISCUSSION

Our patient is typical in the indirect manner of presentation on repeated occasions. Unfortunately, the gold standard of diagnosis, angiography, failed to provoke specialist referral at a time when the prognosis was more favorable. He suffered deteriorations paralleled by raised inflammatory markers, as occurs in 85% of Takayasu patients[3]; his disease course was compatible with the current view of Takayasu arteritis gleaned from larger case series[3,4]: A relapsing pattern of active arteritis, which may persist histologically despite apparent clinical remission. Use of steroids alone brings a recurrence rate of up to 45% and a requirement for further cytotoxic therapy to control disease in 40%[5]. Experience of such cases has led us to advocate treatment with pulsed intravenous steroids and cyclophosphamide, using methotrexate for maintenance therapy where appropriate[6,7].

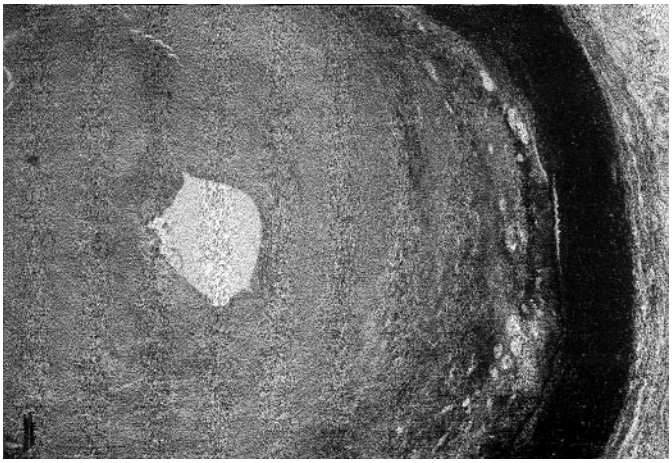

Figure 1. Coronary artery exhibiting marked fibrous intimal proliferation, as seen in chronic atheroma.

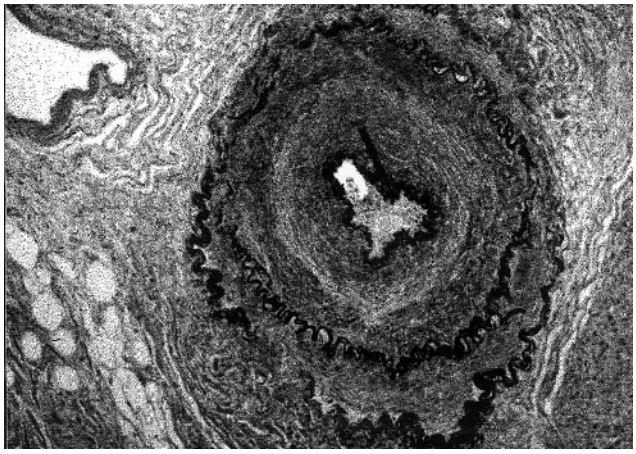

Figure 2. Aortic vasa vasorum showing disruption of elastic laminae consistent with vasculitis. The adjacent aorta shows mild changes of intimal thickening.

We hypothesize that inadequate targeting or suppression of the immune mediators that give rise to endothelial damage in vasculitis may result in rapid progression to atherosclerotic disease, a process that is acknowledged to be dependent upon immune mechanisms[8]. The recent description of endothelial dysfunction, an early marker for atherosclerosis[9], in patients with systemic vasculitis lends support to this hypothesis[10]. Endothelial dysfunction *in vivo* may therefore be a marker for early vascular insult, leading to the common endpoint of atherosclerosis. Our young patient demonstrated classical atherosclerotic plaques in the aorta at post mortem, as could be expected in a man with preexisting cardiovascular risk factors. However, upper body lesions occurred with a distribution and gross morphology typical of Takayasu arteritis that were histologically indistinguishable from those of atherosclerosis. We would argue that this picture represents a rapidly progressive atheromatous process in the context of persisting, uncontrolled inflammatory activity.

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