EDITORIAL

CLASSIFICATION AND TREATMENT OF SYSTEMIC VASCULITIS

The vasculitides are a heterogeneous group of uncommon diseases characterized by inflammatory cell infiltration and necrosis of blood vessel walls. They may arise de novo (e.g. polyarteritis nodosa), or on the background of an established clinical disease (e.g. rheumatoid arthritis). There is no widely accepted classification of vasculitis though most are derived from that by Zeek [1] who described five distinct entities: hypersensitivity angiitis, allergic granulomatous angiitis, rheumatic arteritis, periarteritis nodosa and temporal arteritis. A simpler classification reflects the major clinical consequences of vasculitis (which depend on the size, site and inflammatory response of the affected vessels) and contracts Zeek’s classification into three broad groups [2, 3].

I. Systemic necrotizing arteritis of small and medium sized arteries: (a) polyarteritis nodosa group (classical polyarteritis, arteritis of connective tissue diseases etc.); (b) arteritis associated with granulomatosis (Churg–Strauss vasculitis, Wegener's granulomatosis).

II. Small vessel hypersensitivity vasculitis involving capillaries and venules (Henoch–Schönlein purpura, essential mixed cryoglobulinaemia, vasculitis of connective tissue diseases etc.).

III. Large vessel giant cell arteritis (temporal arteritis, Takayasu’s arteritis). This classification also reflects different therapeutic approaches.

Diseases in group I are usually treated with immunosuppressive drugs (especially cyclophosphamide) as well as steroids; group II are often managed conservatively with steroids only in selected cases, and group III are usually controlled adequately with steroids alone.

There is considerable overlap even between these broad classification groups. Palpable purpura due to small vessel leucocytoclastic vasculitis affects up to 20% of patients with polyarteritis nodosa [4–7]. Necrotizing arteritis can involve the temporal arteries mimicking giant cell arteritis [8, 9] and giant cell arteritis has been described affecting smaller arteries in the breast [10] as well as the important posterior ciliary artery of the eye leading to blindness. Classification of difficult cases depends on identifying the largest vessel involved and the dominant histological abnormality.

Localized vasculitis produces particular problems in classification and depends on the absence of systemic symptoms together with accurate histological diagnosis. Localized polyarteritis nodosa has been described in the gall bladder, uterus and skin [6, 11–13]. Whether any of the described cases is truly localized to an individual vessel is debatable, but the lack of progression of cutaneous polyarteritis in long term studies emphasizes that these cases should be classified and treated differently to their systemic counterparts. The concept of localized giant cell arteritis is more difficult. Most cases have arteritis restricted to the head and neck but sporadic reports of giant cell arteritis at other sites including the aorta, breast and skin have been described [10, 14, 15]. The most convincing case of localized giant cell arteritis was reported in this journal and described mesenteric arteritis leading to bowel perforation [16]. Although the patient was initially ill, there was no evidence of giant cell arteritis at other sites and she remained well after surgery, requiring no drug therapy during an 18 month follow-up. Such cases stress the importance of the word ‘systemic’ in the classification of arteritis and the importance of detailed investigations, including histology, before embarking on potentially harmful drug treatment.

Rheumatoid vasculitis also involves a wide range of vessels [17] from digital capillaries to medium sized arteries (nailfold infarcts to bowel perforation/coronary arteritis etc.) and can be classified in groups I and II. It is surprising, therefore, that Hitter and colleagues were recently the first to document properly a case of abdominal microaneurysms detected by angiography in a patient with rheumatoid arthritis [18]. Single aneurysms have been described by angiography and on biopsy specimens [19, 20] and we have seen ‘arteritic’ changes at angiography in four of 11 angiograms in patients with severe systemic rheumatoid vasculitis. Rheumatoid vasculitis can now be added to the expanding list of vasculitic diseases associated...
with microaneurysms, including Churg-Strauss vasculitis, Wegener’s granulomatosis, atrial myxoma, systemic lupus erythematosus and bacterial endocarditis as well as polyarteritis nodosa.

Cyclophosphamide is now accepted as the treatment of choice of Wegener’s granulomatosis [21]. It is also considered by many to be the most appropriate drug for treating the whole systemic necrotizing arteritis group [4, 6, 7, 22, 23], improving survival in polyarteritis nodosa from 50% (steroids alone) to 80% with a combination of steroids plus cyclophosphamide. However, one or two units still question the use of cytotoxic drugs in systemic vasculitis [5, 24] and the recent review of 165 patients with polyarteritis nodosa and/or Churg–Strauss vasculitis studied over the last 25 years by Guillevin et al. [25] attempts to address this problem. Between 1963 and 1973, they treated 65 patients with steroids alone, 48 patients were treated with steroids plus cytotoxics (22 cyclophosphamide) from 1973 to 1979 and 46 patients were treated with steroids plus plasma exchange and randomly allocated to receive this treatment alone, or in addition have cyclophosphamide between 1980 and 1983.

The overall conclusion by Guillevin et al. was that cyclophosphamide conveyed no statistically significant benefit to prognosis. However, their data suggest some possible biological benefit because 'cyclophosphamide plus steroids' had a 76% survival at 3 and 5 years, whereas 'steroid only' survival fell from 70% at 3 years to 59% at 5 years. This represents seven deaths on steroids between 3 and 5 years compared with no deaths on steroids plus cyclophosphamide during this period. This discrepancy was not discussed in the paper, nor were the possible causes for the late deaths which include long term steroid side effects as well as inadequate disease control.

The comparative study showed similar survival rates in both groups (82% with plasma exchange, steroids and cyclophosphamide, 77% with plasma exchange and steroids alone). The use of plasma exchange makes assessment of the potential benefit of cyclophosphamide difficult to determine as long term plasma exchange alone may be immunosuppressive and has been used successfully to treat polyarteritis [26].

Several questions still remain unanswered.

1. Can steroids alone be used to treat polyarteritis nodosa or do they merely suppress 'smouldering disease', leading to a risk of later relapse as suggested by Fauci et al. [27]?
2. Can steroids be used to treat subgroups of patients with systemic necrotizing arteritis such as those with Churg–Strauss vasculitis [28]?
3. If cytotoxic drugs are used what is the most appropriate treatment regimen?

Despite the results of the French study, the literature strongly supports the use of cyclophosphamide and we personally favour an intermittent intravenous or oral regimen [23, 29] because of good patient tolerance, and few side effects as well as effective therapeutic responses. Steroids alone have a significant long term morbidity and may increase the risk of developing vasculitis, especially as a complication of rheumatoid arthritis [30]. It seems important, therefore, for those who favour steroids alone to undertake appropriate comparative studies which avoid historical controls to assess the exact role of corticosteroids with or without cyclophosphamide in the treatment of systemic necrotizing arteritis.

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REFERENCES
SJÖGREN'S SYNDROME: A HUMAN MODEL OF AUTOIMMUNITY AND MALIGNANCY

Sjögren's syndrome (SS) is a common, chronic autoimmune rheumatic disease with strong female preponderance [1, 2], possessing unique features that make it suitable for research of the pathogenesis of both autoimmunity and malignancy. These include:

1. The occurrence of the disease alone—primary Sjögren's syndrome (pSS)—or in association with almost all other autoimmune diseases—secondary (sSS) [3].
2. A wide clinical spectrum, expanding from an exocrinopathy to a systemic process and which in 10% can evolve to B-cell neoplasia [2].
3. A slow progression, averaging 8–10 years from the initial complaints to the well recognized clinical picture of the syndrome [4].
4. The prevalence of pSS in the general population is unknown. A study from Great Britain reported a 3.3% frequency in a geriatric population, but without histological confirmation [5]. A recent study of 62 residents of a Greek nursing