THORAX

Editorials

New perspectives in Wegener's granulomatosis

Wegener's granulomatosis has been recognised as a distinct clinicopathological entity for the past 60 years.[1] It has been differentiated from other systemic vasculitides by its distinctive histopathological features and its predilection for the lungs, upper respiratory tract, and kidneys. Following the initial descriptions of the syndrome greater understanding of its nuances and the apparent importance of cytotoxic medication in treatment has emerged.[2 3]

The last two years have witnessed a broadening of our understanding of Wegener's granulomatosis—in particular a better understanding of the range of presentations and of the natural history of the disease in treated patients, of the role of newer imaging techniques, and of the pathophysiological and diagnostic role of antineutrophil cytoplasmic antibodies (ANCA).

Presentation, complications, and natural history of treated disease

In 1992 Hoffman *et al*[4] presented their updated analysis of 158 patients with Wegener's granulomatosis and the results of the standard National Institutes of Health treatment protocol. Cyclophosphamide was normally given in a dose of 2·0 mg/kg/day, but with up to 5·0 mg/kg/day in some cases because of rapidly progressive disease. It is continued for one year after complete remission is achieved and is then tapered in 25 mg decrements every two to three months. Prednisone is usually started at 1·0 mg/kg/day but as much as 50 mg/kg/day may be given to patients with rapidly progressive disease. The drug is given daily for four weeks and then tapered to 60 mg every other day, and after that further reduced if clinical indices are favourable, until the patient is receiving cyclophosphamide alone.

The value of the review of Hoffman *et al* lies not so much in new data as in its scope and breadth. The range of presenting manifestations seen echoes that in other recent studies.[5] It emphasises, however, the variability and aggressiveness of the disease before its diagnosis. Indeed, although 42% of patients were accurately diagnosed within the first three months, in many, particularly those without renal manifestations, the disease followed a confusing and indolent course for up to 16 years before a definitive diagnosis was established.

The National Institutes of Health series also highlights the relentless progression of organ destruction that may occur in these patients. Most patients had signs and symptoms of upper airway disease at onset but only 45% had intrapulmonary disease. Eventually, however, lung disease developed in 85%. Similarly, only 18% had evidence of renal disease at onset but 77% progressed to develop frank glomerulonephritis within two years; and whereas only 15% had ocular disease initially 52% went on to show some sort of ocular abnormality—particularly proptosis.

The third and most important area highlighted in the paper of Hoffman *et al*[4] relates to the extended follow up of treated patients. Overall the use of cyclophosphamide and prednisone as outlined above resulted in a complete clinical remission in 75% of patients and a partial remission in another 16%. Most of these changed to alternate day corticosteroids relatively quickly (median 3·2 months) and were off corticosteroids within one year. Nevertheless, it took a median of 12 months before a complete remission was obtained despite aggressive chemotherapy. In those 90 patients followed for at least five years complete remission was achieved at least once in 96%. Half of these, however, later experienced at least one relapse. A large subset of patients had enjoyed disease free remissions of five or 10 years but suffered surprisingly high late relapse rates of 13% and 20% respectively. During the period of active disease and its treatment disease related complications relentlessly accumulated and led to permanent disability or morbidity in 86% of the patients.

The range of toxic effects related to treatment was what might have been expected from the regimen used but the 43% overall incidence is alarming. The frequencies of cyclophosphamide induced cystitis (43%), bladder cancer (2·8%) and myelodysplasia (2%) in particular were higher than had been previously reported[3] while the odds ratio for developing a bladder tumour was 33 and for a lymphoma 11—all of these occurring one to eight years after the start of cyclophosphamide. The expected range of corticosteroid related side effects were also seen in this series and a clear relationship between the risk of infection and the use of corticosteroids was demonstrated. Specifically, 50% of all infections due to bacteria, pneumocystis, and fungi occurred during daily corticosteroid therapy; only 20% occurred during alternate day therapy, 16% during therapy with cyclophosphamide alone and 12% during periods of no therapy.

In summary, there is a huge variation in the presentation of Wegener's granulomatosis, which is often atypical with the disease taking an indolent course. The tendency of these patients to relapse even after state of the art treatment and the excessive cumulative morbidity related both to the disease and to treatment are of great concern.

Imaging

During the 1970s and 1980s several studies have addressed the now well known radiographic manifestations of Wegener's granulomatosis.[5–8] A recent presentation of eight patients at Johns Hopkins Hospital delineates some unique pulmonary features of the disease as shown by computed tomography.[9] In addition to clearly showing nodules, cavities, scarring, and spiculation, computed tomography beautifully identified the vasculitic nature of the illness.[7–9] The two most useful radiographic signs were firstly, blood vessels leading to nodules and cavities (feeding vessels) and secondly, small peripheral, wedge shaped densities suggesting pulmonary microinfarction. Although these latter two findings have been described previously in patients with pulmonary thromboembolism[10] and metastatic disease[11] they have not previously been associated with pulmonary vasculitis. Similarly, a recent case report of Churg-Strauss vasculitis convincingly showed enlarged, irregular, stellate pulmonary arteries by high resolution

computed tomography.[12] These two reports suggest that conventional and high resolution computed tomography of the chest may permit earlier diagnosis of some patients with cryptic presentations of pulmonary vasculitis.

Antineutrophil cytoplasmic antibodies

Antineutrophil cytoplasmic antibodies (ANCA) were first reported in 1982 in patients with glomerulonephritis but with no evidence of immune deposits.[13] Subsequent work by van der Woude *et al* defined the sensitivity and specificity of ANCA in the diagnosis of Wegener's granulomatosis and microscopic polyarteritis nodosa (reviewed by Jennette and Falk[13]). Two types of ANCA were found, cytoplasmic (c-ANCA) and perinuclear (p-ANCA).

Data presented during the past three years suggest that these antibodies not only identify a specific subpopulation of patients with systemic vasculitis but may have a central role in pathophysiology. In 1990 Falk *et al*[14] showed a striking effect of ANCA on in vitro neutrophil function. The addition of c-ANCA or p-ANCA serum or of purified ANCA IgG to neutrophils stimulated both oxygen radical production and degranulation, an effect not seen with normal serum or normal purified IgG. These effects were augmented in neutrophils pretreated with tumor necrosis factor. Flow cytometry showed the migration of one ANCA antigen, myeloperoxidase, from its normal location in the primary granule to the surface of the neutrophil after pretreatment with tumour necrosis factor. The authors postulated that ANCA are probably central to the pathogenesis of Wegener's granulomatosis and microscopic polyarteritis nodosa. Their specific hypothesis was that a viral or other infectious illness, which so often precedes the onset of clinical Wegener's granulomatosis, leads to the production and release of cytokines, including tumour necrosis factor. Exposure to these cytokines then allows the migration of myeloperoxidase and other constituents of the neutrophil primary granule to the surface of the neutrophil. The presentation of these antigens on the neutrophil's surface then leads to production of ANCA. Finally, ANCA, interacting with primed neutrophils, stimulate the production of oxygen radicals and the release of more granular constituents, resulting in necrotising vasculitis.

Two recent papers support this hypothesis. In the first Baltaro *et al*[15] examined bronchoalveolar lavage specimens for the presence of ANCA. On the basis of the known correlation of ANCA titre and disease activity[16] of previously identified neutrophilic alveolitis in the bronchoalveolar lavage fluid of patients with Wegener's granulomatosis[17] and of Falk's data (see above)[14] the authors postulated that ANCA might be produced locally. They showed that patients with circulating ANCA also had ANCA of the same immunofluorescent staining pattern in their bronchoalveolar lavage fluid and that the level in the lavage fluid correlated with disease activity. They also demonstrated that in active disease the IgG ANCA: albumin ratio in lavage fluid was increased more than the ratio in serum, suggesting that ANCA were produced by the respiratory lymphoid system. We hope that evidence will be produced that will show whether lavage neutrophils in patients with Wegener's granulomatosis do show evidence of cytokine induced activation such as that found by Falk *et al* in vitro,[14] and whether an increase in IgG ANCA in lavage fluid identifies those patients with ANCA positive systemic vasculitis who do in fact have clinical pulmonary disease.

The second line of evidence supporting the hypothesis of Falk *et al*[14] on the pathogenetic role of ANCA comes from Tervaert and associates.[18] These authors had previously found[19] that ANCA were seen in 93% of patients with active Wegener's granulomatosis, and they noted that during their 16 month prospective study 17 of 35 patients relapsed. All relapses were preceded by a substantial rise in the ANCA titre. The authors set out to assess whether treatment based on a rising ANCA titre rather than on clinical evidence of relapsing disease might prevent clinical relapse.[18] A fourfold increase in ANCA titre or the development of a titre of 1/32 in a patient with a previously negative one was deemed clinically significant. Patients were randomised to be treated for their rising titre ("serological relapse") or to receive no treatment until clinical evidence of relapse developed ("clinical relapse"). Treatment consisted of the addition of cyclophosphamide at 1·0 mg/kg/day and prednisolone at 30 mg/day. If the patient had already been taking either or both drugs the cyclophosphamide dose was increased by 1·0 mg/kg/day (maximum 75 mg/day) and prednisolone was added or increased at the rate of 30 mg/day.

Fifty eight patients with Wegener's granulomatosis were screened for evidence of active disease. By the time the study began 25 patients had already experienced a clinical relapse. In an additional 20 ANCA rose in the course of two years. Fourteen of the 20 were still receiving immunosuppressive treatment, and 13 of these showed rising ANCA within three months of a reduction in the dose of prednisolone or cyclophosphamide.

The apparent benefit of treating a rising titre of ANCA in this study was clearcut. A "clinical relapse" developed in nine of the 11 patients with a rising titre within six months. In patients randomised to receive treatment for "serological relapse," however, there were no early or late clinical relapses. Additionally, those patients randomly assigned to early treatment had lower cumulative doses of cyclophosphamide and prednisolone than patients randomised to have treatment only for "clinical relapse"—most of whom eventually required treatment on clinical grounds. Treatment related side effects in this two year study were mild but were much less frequent in the "serological relapse" group than in the "clinical relapse" group. It is important to remember, however, that in many patients a rise in ANCA titre will not lead to a clinical relapse for several months and, in a few, for up to two years. None the less, it is to be hoped that future data will confirm this study and allow us to treat patients for "serological relapse" with the prospect of avoiding both the relentless clinical relapses and the treatment related morbidity shown in the study of Hoffman *et al*.[4]

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