MATTERS ARISING

Small intestinal bacterial overgrowth in patients with rheumatoid arthritis

I read with interest the paper by Henriksson et al., in which the authors demonstrated an altered character in the small bowel’s bacterial flora in patients with rheumatoid arthritis. However, the authors did not demonstrate the presence of bacterial overgrowth. The syndrome of bacterial overgrowth is characterised by diarrhoea, with malabsorption. The mechanism by which the bacterial overgrowth causes symptoms is not known. These symptoms are related to an increase in the luminal bacterial flora and the presence of obligate anaerobes (colonic luminal flora) as judged by jejunal fluid culture or breath tests. The patients in the study did not have any evidence of malabsorption or diarrhoea.

The investigations used, apart from the bile acid deconjugation test, had not been previously validated in patients with bacterial overgrowth. Quantitative bacterial culture was not done; the bacterial flora was of oral type, not colonic. The presence of enterobacteriaceae (a facultative anaerobe), tryptophic activity, gas production (both not specific to obligate anaerobes) and the use of jejunal biopsy culture (biopsies culture produces different flora than fluid culture) are not proven features of bacterial overgrowth of the small bowel. The controls used did not have the syndrome of bacterial overgrowth as they were not deficient in gastric acid secretion. These flora are associated with an altered and increased bacterial flora, does not necessarily cause symptomatic bacterial overgrowth. Thus only the three patients with positive bile acid deconjugation tests could be considered to have investigational evidence of bacterial overgrowth. In view of previously reported changes seen in the small bowel’s bacterial flora of elderly and infirm people,1 perhaps the findings were not surprising considering the multi-system involvement of rheumatoid arthritis. To confirm their hypothesis that disease activity is due to and not causing the bacterial flora changes, the authors could have studied the influence of either proton pump inhibitors or antibiotics on disease activity.

Relapsing polychondritis as a secondary phenomenon of primary systemic vasculitis

Papo et al recently reported that in 33 patients with relapsing polychondritis (RP) low titre of c-ANCA was found in 24% of the cases. They concluded that low titres of c-ANCA therefore are not specific for Wegener’s granulomatosis (WG). We do not think that this line of reasoning is correct. We and others have earlier reported that c-ANCA is a highly specific and sensitive marker for WG.2 3 Thus we conclude that the presence of ANCA in RP, may instead indicate, that polychondritis occurs in the context of a primary systemic vasculitis (PSV), for example, WG.

We have seen such an association of PSV with polychondritis in six of seven patients with RP (three women, four men).4 The diagnosis of RP was either made histologically or according to the diagnostic criteria established by McAdam et al.5 In six patients, RP presented as a secondary phenomenon during an active phase of a primary vasculitic entity. Autoantibody screening revealed cANCA (PR3 ANCA +) in two patients, pANCA in one patient and autoantibodies to native collagen type II in four patients.5 6 According to the Classification-Criteria for PSV 1990, the underlying PSV in these six patients was: histologically proven WG (PR3 ANCA +) in two cases, microscopic polyangiitis in three cases (one pANCA +), classic polyarteritis nodosa in one case (table).

We think that polychondritis can be diagnosed more often as a secondary phenomenon in PSV than has previously been recognised. The diagnosis of PSV has been considerably improved by the detection of ANCA and the establishment of ACR-Classification-Criteria for PSV 1990,7 and defences for PSV. Subsequently, PSV with secondary polychondritis seems to be recognised more often. Although there are only very few case reports on the association of RP with recognised, classified PSV,8 9 the coincidence of RP with unclassified vasculitic symptoms is said to be about 10%.10 The occurrence of glomerulonephritis in RP seems to be even more frequent (29 of 112 patients).9 These vasculitic symptoms may be attributed to an underlying PSV, that has not previously been recognised as such. We conclude that the occurrence of ANCA in RP should encourage thorough investigation for the presence of PSV, in which the polychondritis may be a secondary phenomenon. This is important, as the vasculitis determines the therapy and prognosis of the disease.
Table 1: Vasculitic organ involvement and immunological features in patients with primary or secondary RP

<table>
<thead>
<tr>
<th>Patient</th>
<th>Organ involvement</th>
<th>cANCA</th>
<th>pANCA</th>
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<td>B, N, H</td>
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Extended ELK-Classification (Nölle et al 1989): B = constitutional symptoms, E = ENT, Ey = eye, G = gastrointestinal, mPA = microscopic polyangiitis, cPAN = classic panarteritis nodosa, RP = relapsing polyangitis.


AUTHORS' reply. In their series of seven patients with relapsing polyangitis (RP), Handrock and Gross could detect ANCA in six patients, two with Wegener's granulomatosis (WG), three with microscopic polyangiitis and one with classical polyarteritis nodosa. They conclude that the presence of ANCA in RP indicates that polyangitis might occur as a second event of a primary systemic vasculitis. Our experience is very different. Among our 12 biopsy positive RP patients, we had only vasculitis. Among these three, WG could be diagnosed in only one with low titre (1/20) pANCA. The other two, one with C-ANCA and one with P-ANCA, had minor cutaneous involvement and no visceral involvement. Among our 25 ANCA-negative patients, nine had vasculitis (cutaneous in seven, quiescent WG in one, mononeuritis multiplex in one). These data indicate that ANCA may be detected in RP without defined systemic vasculitis, including microscopic polyangiitis. In the Mayo Clinic experience, eight of 22 patients with RP had had ANCA with perinuclear or nuclear pattern. Such discrepancies might result from recruitment bias and/or differences in the size of the studied groups, but also from the major problem of diagnostic procedures which require further studies.

We agree with the authors of this study that the diagnosis of RP might be complicated by renal involvement and that the diagnosis of WG in RP patients might be delayed, leading to underdiagnosis of this disease. However, we believe that our approach of establishing a diagnosis of WG in these patients is justified, as the clinical and immunological features strongly suggest a diagnosis of WG.

Nevertheless, we agree with these authors that chondritis can probably occur as an epiphhenomenon in RP rather than being due to definite inflammatory disorders. This is true not only for primary systemic vasculitides, but also for systemic lupus erythematosus, possibly for rheumatic diseases, and even for lepromatous (L++) leprosy. In these circumstances, cartilage involvement frequently differs from the typical features of RP, regarding the usual sparing of the respiratory tree and the lack of a relapsing/remitting course of disease. Unfortunately, aetiological and immunological data on auricular chondritis is rare.

A clear-cut categorisation of patients with vasculitic manifestations and chondritis seems impossible. Definitions of RP, WG and other arthritis and episcleritis can remain purely descriptive of clinical symptoms and pathological data that sometimes overlap, in the absence of a comprehensive view of their pathophysiology and aetiology. Recent studies on ANCA have provided new and promising insights into the processes involved, but their application to diagnosis is mainly restricted to the close association of WG with ANCA, including proteinase 3 which are constantly negative in our patients with RP. Computer-derived criteria for the classification of vasculitides, such as those developed by the American College of Rheumatology, are based on large studies but not particularly relevant for individual patients, especially in the discussion of overlaps between diseases sharing many manifestations. For example, a patient with a typical history of WG, including arthritis and episcleritis, can be classified as RP if auricular chondritis occurs, according to the empirical criteria used by Michet.

Finally, some practical conclusions can be drawn.

1. In most cases RP is a primary disease, even in the presence of vascular manifestations. It should not be considered or treated as a vasculitis on the basis of ANCA positivity. Moreover, there might be some rare cases where patients share manifestations of RP and WG. Due to the poor response of WG to steroids alone, first-line regimes used in such patients with RP/WG overlap should probably include additional cyclophosphamide.
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