MATTERS ARISING

Pigmented villonodular synovitis

I write with regard to the paper by Zuber and colleagues that purports to demonstrate a case of pigmented villonodular synovitis (PVNS).[1]

The pathology material presented by the authors, however, is not diagnostic of PVNS, in that the cellular infiltrate did not demonstrate the large polyhedral cells—usually dubbed histiocytes—that are requisite for the diagnosis of PVNS. Villi, nodules, giant cells, and haemosiderin are not specific, and may be seen in a variety of conditions other than PVNS. It is the histiocyte that renders the pathology of PVNS unique and diagnostic. Indeed, Lichtenstein has described PVNS as a 'histiocytosis' of the synovial membrane.[2]

In addition, the authors suggest that in their patient PVNS was found to affect the second to fifth MCP joints. However, the diffuse form of PVNS is nearly always monarticular; documented cases of polyarticular (usually biarticular) involvement by PVNS are exceptionally rare, and probably number less than half a dozen in the medical literature.

The patient under discussion—who presented with progressive, bilateral ulnar deviation at the MCPs—most probably had rheumatoid disease, not PVNS. If there is a 'lesson' to this case, it is that the correct diagnosis of an unusual condition such as PVNS requires awareness of the characteristic clinical presentation of the disease and attentiveness to its diagnostic histopathology.

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1 Zuber M, Braun C, Pfreundschuh M, Puschel W. Ulnar deviation is not always rheumatoid. Ann Rheum Dis 1996;55:786-8.
2 Lichtenstein L. *Diseases of bone and joints.* St Louis: CV Mosby, 1970: 209.

Author's reply

Dr Docken expresses the opinion that the patient under discussion did not suffer from pigmented villonodular synovitis (PVNS) but from rheumatoid arthritis. Although I do agree that rheumatoid arthritis has to be considered as a differential diagnosis, the described patient did not fulfil the 1987 revised criteria for the classification of rheumatoid arthritis.[1] The patient did not suffer from morning stiffness in and around joints. She did have swellings of the MCP joints that were asymmetrical—that is, far more prominent on her left side; no signs of arthritis in these joints were present, however. The symptoms were not symmetrical. The patient did not have subcutaneous nodules, no rheumatoid factor was present in her serum, *x* rays of hands and feet did not show any erosions.

The patient presented in the department of traumatology, hand and reconstructive surgery with a fixed flexion deformity of her left MCP joints, which caused inability to open her hand properly. She did not present with typical symptoms of rheumatoid arthritis such as morning stiffness, tenderness or pain. Synovectomy of the second to fifth MCP joints and reconstruction of the extensor hood of the left hand was performed. The right hand showed discrete thickening of the MCP joints. No need for surgery was discovered there. After surgery the patient was referred to rheumatology. Here the discrepancy between the lack of typical symptoms and signs of rheumatoid arthritis and the severe and asymmetric ulnar deviation, both of which is very unusual, was noted. Because of this discrepancy it was decided to ask for the routinely performed histological evaluation of the operation specimen, which clearly stated that PVNS was present.

The second point Dr Docken raises is the evaluation and interpretation of the histological specimen. His concern is that there might have been no histiocytes present in the specimen. Jaffe, Lichtenstein, and Sutro described in 1941[2] the salient histological features of PVNS, which are deposition of haemosiderin and infiltration of histiocytes and giant cells in a fibrous stroma within the synovium of tendon sheaths and large joints. I agree that it is the fibrohistiocytic proliferation that is characteristic for the pathology of the PVNS. Lipid filled histiocytes, also called foam cells, are depicted in figure 2 of the paper together with giant cells and scattered lymphocytes.

The third issue Dr Docken discusses is the fact that diffuse PVNS tends to occur monarticular. The knee is the most frequent joint involved, followed by the hip and ankle. Infrequently, the diffuse form will present in the hand, shoulder, wrist, and vertebral. Bilateral forms do occur occasionally[3] and polyarticular forms are rare.[4] Recently an unusual case of multiple site involvement of PVNS in a child has been reported.[5] The case presented in our paper belongs to the rare polyarticular forms of diffuse PVNS.

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1 Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
2 Jaffe HL, Lichtenstein L, Sutro CJ. Pigmented villonodular synovitis, bursitis and tenosynovitis. Arch Pathol 1941;31:731-65.
3 Gehweiler JA, Wilson JW. Diffuse biarticular pigmented villonodular synovitis. Radiology 1969;93:845-51.
4 Leszczyxnski J, Huckell JR, Percy JS, LeRiche JC, Lentle BC. Pigmented villonodular synovitis in multiple joints. Ann Rheum Dis 1975;34:269-72.
5 Kay MK, Eckardt JJ, Mirra JM. Multifocal pigmented villonodular synovitis in a child. Clin Orthop 1996;322:194-7.

Combination DMARD therapy for rheumatoid arthritis. Full or low DMARD doses?

We read with great interest the paper by O'Dell.[1] We would like to offer some comments on it. Although we strongly believe in the rationale of the author, we feel that as clinicians our options should be based on clear cut data when treating patients with erosive progressive rheumatoid disease. In our clinical practice, in active and severe diseases, we try to optimise any treatment by using the highest doses of both non-steroidal anti-inflammatory drugs and disease modifying antirheumatic drugs (DMARDs), compatible with an acceptable risk of toxicity. According to the medical literature, in rheumatoid arthritis (RA) the highest doses of OH-chloroquine (OH-C) are 6 mg/kg/day, of methotrexate (MTX) 17.5-20 mg/week, and of sulphasalazine 3 g/day.[2–4] Poor or inadequate responses can be assessed only when these amounts are reached. In the study by O'Dell,[5] three groups of patients were studied, one receiving full doses of MTX, one a combination of full doses of OH-C and 1 g/day sulphasalazine, and the third a combination of the three. To our knowledge no data exist suggesting that the combination of full doses of OH-C plus 1 g day of sulphasalazine is any better than OH-C alone. It might well be that an additive effect is reached by such a combination, but this has never been proved. In addition no proof exists that 1 g/day sulphasalazine from the beginning, is clinically of any value in the long term treatment of RA.

When examining the combination studies that have been published on MTX and OH-C, we found no evidence of a statistically significant clinical or biological additive or synergistic effect of the two drugs. Therefore either the addition of low doses sulphasalazine to the two drugs exerts some peculiar, beneficial synergistic effect, still to be unequivocally proved, or the study lacks the data of a fourth group combining MTX plus 1 g/day sulphasalazine. Possible support for the additive effect, comes from a previously published open study using a combination of lower doses of MTX (mean dose throughout the study: 8.3 mg/week) plus full doses of sulphasalazine (2-3 g/day). The study showed that the association was more beneficial than the monotherapy with MTX alone.[6] In fact while mean values of disease activity score (DAS) decreased by 26% in monotherapy, a mean decrease of 49% was seen in combination therapy. As the initial values of DAS were 5 or more, the results at the sixth month were certainly statistically significant, although of uncertain clinical importance. In contrast, in the O'Dell study[5] the difference between groups, arose only after the 8-10th month of treatment with the multiple combination.

Therefore the real part in clinical practice, played by several combinations with low or full doses of each molecule, needs to be unequivocally confirmed.

Few studies have used full doses of single drugs or of various drugs in combination for long periods of time. Some negative results, at least, could have resulted from low doses or the results with single drug therapy could have been improved by using full doses of the drug.

As clearly hypothesised by O'Dell, by using full doses of the available drugs, the results should be even better either in terms of time lapse before the appearance of the response or of the degree of the response. We also need a clear distinction among the patients, between those who improve in a clinically meaningful manner (50% or more) and those who survive while receiving treatment without such a significant clinical benefit. For example, in our own experience with MTX, only 37% of 159 patients with active, erosive RA, followed up for three years, had a clinically important response,[7] even though 83% were still receiving the drug (Ferraccioli