Annals of the
RHEUMATIC DISEASES

Leader

Rheumatoid arthritis, malignancy, and paraproteins

Rheumatoid arthritis and malignancy

Mortality is increased in patients with rheumatoid arthritis (RA),[1] and large surveys of patients with reticuloses[2] or RA[3] have shown firm evidence of an association between lymphoma and RA. Further support for this association was also obtained from a large population study in Finland in 1982,[4] where an excess of Hodgkin's disease, non-Hodgkin's lymphoma, myeloma, and leukaemia was shown in patients with RA. The association between lymphoma and RA seems to relate more to duration of disease than severity,[5] with the mean interval between the onset of RA and the development of lymphoma in one series being 17 years.[6]

The coexistence of RA and plasma cell dyscrasia was well recorded by Galli and Chiti in 1955,[7] but they found some difficulty in separating the clinical features of each disorder. A relation between RA and myeloma was proposed in 1969 by Zawadzki and Benedek after a careful review of published work to which they were able to contribute six patients with both RA and a monoclonal gammopathy who had developed myeloma.[8] At the same time an increased incidence of RA among 112 unselected patients with plasma cell and lymphocytic neoplasms was reported,[9] supporting the contention that the risk of plasma cell disorders is increased in patients with RA. A year later five further patients with longstanding RA who subsequently developed myeloma were reported.[10] Interestingly, it was noted that joint symptoms improved in each case after treatment with melphalan. A more recent study with more clearly defined diagnostic criteria has since confirmed the association between RA and myeloma.[11]

Rheumatoid arthritis and paraproteins

The relation between paraproteins and RA has attracted increasing interest and was the subject of a recent editorial,[12] which stressed the need for further research into the relevance of monoclonal gammopathy occurring in patients with rheumatic disease. Paraproteins are immunoglobulins with a narrow electrophoretic pattern due to clonal expansion of light or heavy subclass chains. The increase in globulins may affect several globulin fractions (*polyclonal gammopathy*) or a single globulin (*monoclonal gammopathy*). The latter gives rise to a dense band on electrophoresis. Many conditions are associated with paraproteinaemia, among the best known of which are myeloma, lymphoma, and Waldenström's macroglobulinaemia. The paraproteins associated with these disorders are almost invariably monoclonal. Monoclonal gammopathy has also been reported, however, in a variety of other clinical settings: it has been found in association with a number of primary malignant neoplasms arising from outside the lymphoreticular system; in chronic infections of the chest and biliary tree; and has been noted in patients with several connective tissue diseases in addition to RA. Since serum electrophoresis became generally available 20 years ago, several studies have put the incidence of monoclonal gammopathy in patients with RA at about 1% to 2%,[13 14] compared with that in a general population matched for age of under 1%.[15]

Malignancy and paraproteins

Estimates of the likelihood of an otherwise healthy subject with a paraprotein developing haematological malignancy have varied widely from 0·5% in patients with a low concentration of a stable paraprotein to as many as 28% of elderly patients over a 10 year period. We have recently studied the possible relevance of monoclonal gammopathy as a marker of later malignancy in patients with RA.[16]

Twenty three patients with RA and a monoclonal serum paraprotein were identified and their progress followed prospectively.[16] All patients underwent bone marrow examination and skeletal survey. The diagnosis of RA and discovery of the paraprotein were synchronous in five patients, but in none was the paraprotein found before the onset of joint symptoms. The concentrations of paraprotein detected did not differ significantly between immunoglobulin subclasses. Free light chains were found in the urine of eight patients.

An abnormal bone marrow was found more commonly in patients with an IgA or IgM paraprotein than in those with an IgG paraprotein. The risk of an abnormal bone marrow was no greater in the patients with Sjögren's syndrome or in those with free light chain excretion. At review, which was conducted a median of four years after the initial report of paraproteinaemia, five patients had developed myeloma, of whom three had an IgA paraprotein. Two further patients had developed non-Hodgkin's lymphoma, both of whom had features of longstanding secondary Sjögren's syndrome. Three of four patients with immune paresis developed myeloma, whereas none of the patients with a polyclonal rise in the other immunoglobulins developed malignancy.

Other connective tissue diseases

An increased risk of lymphoma in Sjögren's syndrome was

reported 10 years ago and, although estimates of this risk have varied considerably with the population size and sample, non-Hodgkin's lymphoma seems to occur at least 10 times more frequently than in a control population.[17] It has been suggested that free light chains in the urine might be a useful predictor of later malignancy in patients with primary Sjögren's syndrome,[18] and these can be measured fairly easily. Unlike the position of RA, however, serum paraproteinaemia is considerably more common in patients with Sjögren's syndrome than in a control population. The presence of a serum paraprotein in Sjögren's syndrome may prove to be a more specific marker for later malignancy than urinary paraprotein, a possibility which we are currently investigating as part of a longitudinal study of patients with primary Sjögren's syndrome. Certainly serum paraprotein tends to be found in patients with aggressive systemic disease, which is often associated with lymphadenopathy, and this group of patients seems most likely to develop malignancy. This suggests that patients with RA with secondary Sjögren's syndrome may be at special risk of later lymphoma.

By comparison, haematological malignancy is not a recognised feature of patients with systemic lupus erythematosus (SLE). In a longitudinal study of 415 subjects with SLE nine developed a monoclonal paraprotein. These patients were generally younger and paraprotein concentrations were unrelated to clinical and laboratory measures of disease activity.[19] Bone marrow examination was performed in all nine patients with monoclonal gammopathy and showed no evidence of malignancy in any. None developed malignancy during a mean follow up period of five years. The immunoglobulin and light chain distribution of the paraproteins was as seen in benign gammopathy, with IgG predominant. Reports of fewer than 10 patients with both SLE and myeloma have been published, and there is no evidence of an association between lymphoma and SLE. Hence monoclonal gammopathy does not carry any adverse prognostic implications for patients with SLE, and those with an overlap syndrome with RA ('Rupus') are unlikely to be at any greater risk of lymphoproliferative malignancy than those with 'pure' RA.

Other factors

Both in the elderly population with paraproteinaemia and no associated disease and in patients with myeloma, IgG paraproteins account for the vast majority of monoclonal gammopathies. In RA the distribution seems to be slightly more diverse, with IgA and IgM paraproteins present in up to half of all patients with monoclonal gammopathy. This difference may be of some relevance to the relative risk of developing later malignancy, especially myeloma, where patients with an IgA paraprotein are overrepresented.[16] This may relate to the observations that patients with RA and IgA rheumatoid factor generally have a more aggressive course to their disease,[20] and that IgA rheumatoid factor has been implicated in the development of villous atrophy in patients with RA.[21] Furthermore, immune complexes containing IgA have been detected in the mesangium of patients with RA and glomerulonephritis.[22]

The potential of certain immunosuppressive drugs to produce later malignancy in patients receiving them over a period of several months is well recorded.[23,24] The possibility that immunomodulatory drug treatment in patients with RA might contribute to the excess of lymphoma found in RA has been considered.[25] It seems certain that cyclophosphamide and azathioprine are associated with the later development of an excess of non-Hodgkin's lymphoma, and chlorambucil has been incriminated as a contributory factor in the development of leukaemia. Other cytotoxic drugs in more common use in the United Kingdom and the United States for the treatment of RA—for example, methotrexate—have not been shown to carry any increased risk of haematological malignancy. Care should clearly be taken to minimise the dose and duration of treatment of any cytotoxic agent in patients with RA in order to keep the additional risk of induced malignancy to a minimum.

Polyclonal gammopathy is often found in patients with active RA and may be a marker of systemic disease. A polyclonal rise in immunoglobulins in RA is a non-specific finding, however, with immunoglobulin concentrations fluctuating with time spontaneously or as a result of therapeutic intervention. There do not seem to be any specific associated prognostic implications. In addition to the hypergammaglobulinaemia seen in RA, the marked proliferation of lymphoid tissues, together with the increase in plasma cell numbers and the wide variety of autoantibodies present, all underline the hyperreactivity of the lymphoreticular system in this disease.

Hence, although the incidence of monoclonal paraproteinaemia seems to be only slightly increased in RA, there does seem to be a genuine increase in the incidence of both myeloma and lymphoma in patients with longstanding disease. The explanation most commonly offered for this relates to the chronic immune stimulation of B lymphocytes in the bone marrow of patients with longstanding RA, perhaps by agents such as the Epstein-Barr virus, which are capable of the induction of monoclonal expansion and possibly associated with a reduction in immune surveillance, leading to the production of a monoclonal paraprotein by a mutant strain of differentiated B lymphocytes or plasma cells. These cells may then develop the capacity to become 'malignant', and evidence is accumulating that a relatively high percentage of patients with RA and a monoclonal paraprotein do ultimately develop either myeloma or a B cell lymphoma.

Recommendations

We suggest that monoclonal gammopathy occurring in patients with RA should be promptly investigated with a skeletal survey and a bone marrow study. Elderly patients with disease of long duration seem to be at most risk of malignant transformation, and the presence of an IgA paraprotein appears to carry a special risk of myeloma. Patients with abnormalities on bone marrow examination should probably be followed up every six months to reassess paraprotein concentrations, a significant increase in which should prompt reinvestigation.

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1 Mitchell D M, Spitz P W, Young D Y, Bloch D A, McShane D J, Fries J F. Survival, prognosis and causes of death in rheumatoid arthritis. *Arthritis Rheum* 1986; 29: 706–14.
2 Lea A J. An association between the rheumatic diseases and the reticuloses. *Ann Rheum Dis* 1964; 23: 480–4.
3 Prior P, Symmons D P M, Hawkins C F, Scott D L, Brown R. Cancer morbidity in rheumatoid arthritis. *Ann Rheum Dis* 1984; 43: 128–31.
4 Isomaki H A, Hakulinen T, Joutsenlahti U. Excess risk of lymphoma, leukaemia and myeloma in patients with rheumatoid arthritis. *Ann Rheum Dis* 1982; 41 (suppl): 34–8.
5 Symmons D P M, Ahern B, Bacon P A, *et al.* Lymphoproliferative malignancies in rheumatoid arthritis. *Ann Rheum Dis* 1984; 43: 132–3.
6 Banks P M, Witrak G A, Conn D L. Lymphoid neoplasia developing after connective tissue disease. *Mayo Clin Proc* 1979; 54: 104–8.
7 Galli T, Chiti E. Rheumatoid arthritis and plasmacytosis. *Ann Rheum Dis* 1955; 14: 271–8.
8 Zawadzki Z A, Benedek T G. Rheumatoid arthritis, dysproteinemic arthropathy and paraproteinemia. *Arthritis Rheum* 1969; 12: 555–63.
9 Goldenberg G J, Paraskevas S, Israels L G. The association of rheumatoid arthritis with plasma cell and lymphocytic neoplasms. *Arthritis Rheum* 1969; 12: 569–77.

10 Wegelius W, Skrifvars B, Andersson L. Rheumatoid arthritis terminating in plasmacytoma. *Acta Med Scand* 1970; **187**: 133–8.
11 Katusic S, Beard C M, Kurland L T, Weiss J W, Bergstralh E. Occurrence of malignant neoplasms in the Rochester, Minnesota rheumatoid arthritis cohort. *Am J Med* 1985; **78**: 50–5.
12 Pruzanski W. Rheumatological disorders and monoclonal gammopathy—A new syndrome? *Br J Rheumatol* 1987; **26**: 409–15.
13 Waldenström J. Clinical diagnosis and biochemical findings in material of 296 sera with M-type marrow γ-globulins. *Acta Med Scand* 1961; **170** (suppl 367): 110.
14 Hallen J. Discrete gammaglobulin (M component) in serum. *Acta Med Scand* 1966; (suppl 462): 1–127.
15 Malacrida V, Francesco D D, Banfi G, Porta F A, Riches P G. Laboratory investigation of monoclonal gammopathy during 10 years of screening in a general hospital. *J Clin Pathol* 1987; **40**: 793–7.
16 Kelly C A, Baird G, Foster H, Hosker H, Griffiths I D. The prognostic significance of paraproteinaemia in rheumatoid arthritis. *Br J Rheumatol* 1989; **28** (suppl): A22.
17 Talal N, Bunim J J. The development of malignant lymphoma in the course of Sjögren's syndrome. *Am J Med* 1964; **36**: 529–40.
18 Moutsopoulos H M, Costello R, Drosos A A, Mavridis A K, Papadopoulos N M. Demonstration and identification of monoclonal proteins in the urine of patients with Sjögren's syndrome. *Ann Rheum Dis* 1985; **44**: 109–12.
19 Rubin L, Urowitz M P, Pruzanski W. Systemic lupus erythematosus with paraproteinaemia. *Arthritis Rheum* 1984; **27**: 638–43.
20 Gioud-Paquet M, Auvinet M, Raffin T, *et al*. IgM rheumatoid factor, IgA RF, IgE RF, and IgG RF detected by ELISA in rheumatoid arthritis. *Ann Rheum Dis* 1987; **46**: 65–71.
21 O'Farrelly C, Melcher D, Price R, *et al*. Association between villous atrophy in rheumatoid arthritis and a rheumatoid factor and gliadin-specific IgG. *Lancet* 1988; **ii**: 819–21.
22 Beaman M, Adu D, Howie A J, McConkey B, Michael J, Popert A J. Rheumatoid arthritis and IgA nephropathy. *Br J Rheumatol* 1987; **26**: 299–302.
23 Penn I, Hammond W, Brettschneider I, *et al*. Malignant lymphomas in transplantation patients. *Transplant Proc* 1969; **1**: 106–12.
24 Kinlen L J. Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. *Am J Med* 1985; **78** (suppl 1A): 44–9.
25 Symmons D P M. Neoplasia in rheumatoid arthritis. *J Rheumatol* 1988; **15**: 1319–22.