

CORRESPONDENCE

CD5 positive B cells in peripheral blood and lymph nodes in rheumatoid arthritis

We read the paper by Kondratowicz *et al* with interest, in which it was concluded that the lymphadenopathy and lymphocytosis in rheumatoid arthritis (RA) could be active features of this multiorgan disease.¹ Although the panel of lymphocyte markers used in their study was fairly comprehensive, it did not include CD5 (T1) antigen. Recent documented findings showed that peripheral B lymphocytes of patients with certain autoimmune diseases, including rheumatoid arthritis, express CD5 (T1) antigen, a marker

for T cells and most B lineage chronic lymphocytic leukaemia.^{2,3} We believe that the authors' study should have included CD5 antigen so as to enhance the understanding of lymphoid hyperplasia in rheumatoid lymphadenopathy. A case in which a 68 year old patient with a 20 year history of seropositive rheumatoid arthritis and generalised cervical lymphadenopathy was briefly described⁴; both peripheral blood lymphocytes and those from the lymph node showed a significant increase in CD5 positive B cells.

Histologically, this patient's lymph node showed substantial expansion of the T dependent paracortical zone by a monotonous sheet of lymphoid cells with slightly contorted

nuclei with a narrow rim of cytoplasm (figure and inset). There was spillage of lymphocytes into the perinodal fat. This resulted in compression of the lymphoid follicles. This was unlike most rheumatoid lymphadenopathy which shows lymphoid follicular hyperplasia. Immunohistological examination of the cryostat sections showed striking staining of CD5 positive B cells in the T dependent paracortical zone (fig B) and they coexpressed CD19 antigens (fig B, inset) and were polyclonal for light chain immunoglobulins.

Analysis of the immunofluorescence flow cytometry and immunostaining of the harvested peripheral blood lymphocytes showed similar results. There was a normal range of CD3 positive T cells (53.9%) with 41.8% CD4 T cells and 14.2% CD8 T cells of the total peripheral lymphocyte population (ratio of CD4:CD8 cells = 2.9:1, range 0.9-3.0). Numbers of CD19 B cells were increased at 21.1% (normal range 2-15%) and were polyclonally stained for both surface κ and λ light chain (κ 8.0%, λ 7.3%), with IgM at 0.8%. A striking excess of CD5 positive B cells at 68.5% was also present (fig C).

Based solely on morphology, the lymph node could be highly suspicious of a low grade T cell lymphoma. Moreover, in longstanding autoimmune disease, including rheumatoid arthritis, there is an increased association with lymphomas. Autoantibodies can also be detected in up to one third of patients with B chronic lymphocytic leukaemia.⁵ The findings in this patient with RA and a florid lymphoproliferative "reactive" disorder with overt expression of CD5 positive B cells in peripheral lymphocytes and lymph node represent an aberrant B cell lesion. It is plausible that such aberrant expression of CD5 antigens in B cells in autoimmune disorders could represent a prodrome before the development of clonal restricted B cell lymphomas or leukaemia.

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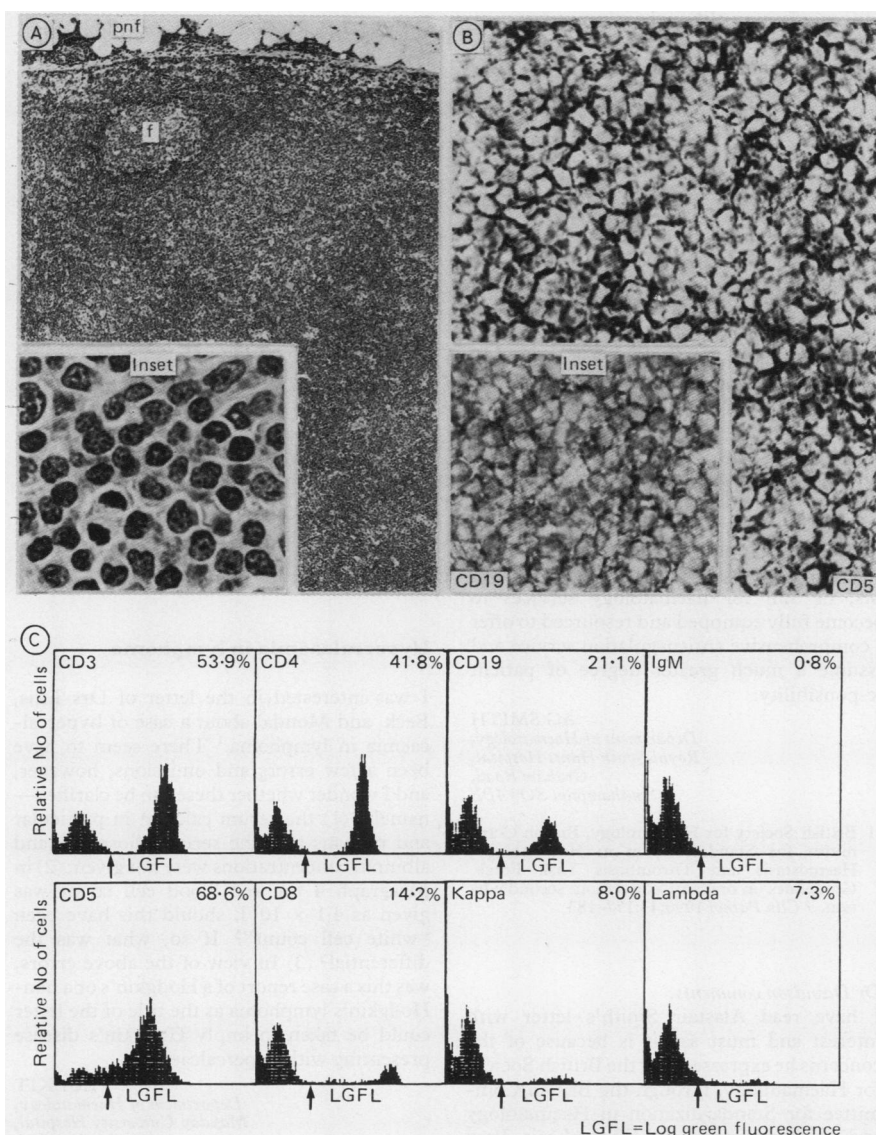
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- 1 Kondratowicz GM, Symmons DPM, Bacon PA, Mageed RAK, Jones EL. Rheumatoid lymphadenopathy: a morphological and immunohistochemical study. *J Clin Pathol* 1990;40:106-13.
- 2 Dauphinee M, Tovar Z, Talal N. B cells expressing CD5 are increased in Sjögren's syndrome. *Arthritis Rheum* 1988;31:642-7.
- 3 Plater-Zyberk C, Maini RN, Lam K, Kennery TD, Janosy G. A rheumatoid arthritis B cell subset expresses a phenotype similar to that in chronic lymphocytic leukaemia. *Arthritis Rheum* 1985;28:971-6.
- 4 Wong SY, Sewell HF. CD5 positive B cells in peripheral blood and enlarged lymph nodes in rheumatoid arthritis—a case report. *J Pathol* 1989;158:339A.
- 5 Galton DAG. In: Hardisty RM, Weatherall DJ, eds. *Blood and its disorders*. 2nd ed. Oxford: Blackwell Scientific Publications, 1982:877-913.

Drs Kondratowicz, Mageed, and Jones comment:

The case described by Wong and Sewell is of considerable interest. The histological features illustrated seem to resemble those in one of our 16 rheumatoid nodes in which there was a considerable expansion of the



Low power field (A) of the lymph node showing expansion of the paracortical zone with compression of the lymphoid follicle (f) and spillage of lymphocytes in the perinodal fat (pnf) (haematoxylin and eosin). Inset shows that most of the lymphocytes have contorted nuclear outlines. (B) CD5 and CD19 (inset) lymphocytes in the paracortical zone (immunostaining/haematoxylin). (C) Flow cytometric analysis of peripheral blood lymphocytes: a cursor was set (↑) using control antibody. Quantitation of lymphocyte expression of antigens shown as percentages was derived from data to the right of the cursor, analysed using the EPICS C computer system.

paracortex and small germinal centres. This was from a patient with systemic vasculitis, a high erythrocyte sedimentation rate, but a low rheumatoid factor titre at the time of biopsy.

We have not yet investigated the possibility that the numbers of CD5 positive B cells are increased in our rheumatoid nodes, but the findings in the case described support our view that rheumatoid lymphadenopathy is likely to be an active part of the disease process. A role for the CD5 B positive cell population in autoimmune diseases has been suggested, based on studies of the Ly-1 positive B cells in murine models of autoimmune diseases, because of their ability to produce autoantibodies which express cross-reactive idiotypes (CRI), encoded by unmutated Ig variable region germ line genes.¹ We have since found (unpublished observations) that increased numbers of plasma cells containing such CRI are associated with rheumatoid factor activity in rheumatoid nodes.^{2,3} It will be interesting to see if surface CRI-bearing B lymphocytes in frozen sections also coexpress CD5, as we have shown that such CRI are highly expressed by CD5 positive B cells in fetal liver and cord blood at a clonal level (unpublished observations).

- Hayakawa K, Hardy RR, Honda M, Herzenberg LA, Steinberg AD. Ly-1 B-cells. Functionally distinct lymphocytes that secrete IgM autoantibodies. *Proc Natl Acad Sci USA* 1984;81:2494-8.
- Mageed RA, Dearlove M, Goodall DM, Jefferis R. Immunogenic and antigenic epitopes of immunoglobulins XVII: Monoclonal antibodies reactive with common and restricted idiotypes to the heavy chain of human rheumatoid factors. *Rheumatol Int* 1986;6:179-83.
- Crowley JJ, Goldfien RD, Schrohenloher RE, et al. Incidence of three cross-reactive idiotypes on human rheumatoid factor para-proteins. *J Immunol* 1988;140:3411-18.

Guidelines on oral anticoagulation: second edition

As a consultant haematologist who no longer takes anticoagulant clinics I read with interest the revised guidelines on oral anticoagulation.¹ Probably the guidelines do represent an advance in that they attempt to standardise and simplify advice on desired INR ratios. It is a pity, however, that they still have to be based on a mixture of fact, fiction, and subjectivity. Even in 1990, so much anticoagulant practice is not based on the results of good, well structured clinical trials.

It is necessary to express a contrary view to the statement that patients taking oral anticoagulants when discharged from hospital should normally be referred to consultant haematologists for the control of outpatient treatment. Given the increasing clinical, laboratory, and managerial commitments of a consultant haematologist, anticoagulant control should assume a low priority. In my own experience control of short and long term anticoagulation can be adequately and safely done by general practitioners after a short, simple education programme.

Where specific problems of anticoagulation arise these are referred for consultant opinion and action. In such a system the

patient benefits in that he or she remains clearly under the supervision of his or her general practitioner who is the person supervising all other treatment. The general practitioner is thus in the strongest position to advise the prescribing specialist as to when and if anticoagulant treatment may have become inappropriate or present an undue hazard in any one patient.

It is usually argued that haematologists should be involved in anticoagulant control because "the haematologist does it better". Doubtless, minute precision of INR control may be improved but it is also likely that any other person trained exclusively to take anticoagulant clinics can similarly maintain a high level of INR precision. Whether such precision represents an improvement in the totality of individual patient care for the investment involved is quite another matter. Certainly, as a generalisation, for 90% of patients taking anticoagulants at least 90% of the time there is no major problem; when problems arise they are generally difficult whoever is involved in supervising anticoagulation, although it must be conceded the haematologist in this situation is usually in the best position to give clear advice as to practical short term management.

Despite good intentions most anticoagulant clinics end up as a thoroughly unsatisfactory professional experience. This is because they deliberately set out only to take responsibility for anticoagulation and not other clinical problems, such limited responsibility often confuses the patient and other groups of doctors. If haematologists should be the people running anticoagulation it would be better for them to have sufficient resources to have total specialist control of all such patients and firmly establish policies regarding duration of anticoagulation, indications, etc.

Surely it is time to take a step forward and either actively demythologise anticoagulant treatment and encourage general practitioners to take responsibility for anticoagulant control, with appropriate availability of support and help from consultant haematologists, or aim for haematology services to become fully equipped and resourced to offer a comprehensive anticoagulation service and assume a much greater degree of patient responsibility.

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- British Society for Haematology, British Committee for Standardization in Haematology, Haemostasis and Thrombosis Task Force. Guidelines on oral anticoagulation: second edition. *J Clin Pathol* 1990;43:177-183

Dr Davidson comments:

I have read Alastair Smith's letter with interest and must say it is because of the concerns he expressed that the British Society for Haematology, through the British Committee for Standardization in Haematology and its Haemostasis and Thrombosis Task Force, felt it necessary to issue guidelines on oral anticoagulation in an attempt to improve standards of clinical practice.

Yes, clinical trials are limited. The recommendations are based on available scientific data, plus a consensus of United Kingdom practice.

Beware of anticoagulant control becoming a "low priority" and "a thoroughly unsatis-

factory professional experience" for a consultant haematologist—not very reassuring to the 0.25 million plus patients receiving this treatment in the United Kingdom.

Rather, "aim for haematology services becoming fully equipped and resourced to offer a comprehensive anticoagulant service and assume much greater degrees of patient responsibility".

I do not think we are really at odds with Alastair Smith. I am sure he wishes to provide these patients with a high standard of service. That is what the guidelines are all about. Maybe he needs to persuade his general manager to provide the necessary resources—the guidelines will help in this respect.

Examination of faeces for bacterial pathogens

We wish to draw your attention to a simple error in the ACP Broadsheet "Examination of faeces for Bacterial Pathogens".¹ In the section dealing with isolation of *Staphylococcus aureus* it is stated that colonies of this organism will appear pink on mannitol salt agar. We suspect that most laboratories will use phenol red as a pH indicator—those using the Oxoid formulation are obliged to do so as it is present in the medium as supplied. Mannitol-fermenting colonies are yellow on phenol red-containing media.

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- Pedler SJ, Orr KE. Examination of faeces for bacterial pathogens. *J Clin Pathol* 1990;43:410-15.

Hypercalcaemia in lymphoma

I was interested in the letter of Drs Ellis, Beck, and Mondal about a case of hypercalcaemia in lymphoma.¹ There seem to have been a few errors and omissions, however, and I wonder whether these can be clarified—namely, (1) the serum calcium in particular and perhaps also the serum phosphate and albumin concentrations were not given; (2) in paragraph 4 the red blood cell count was given as $4.1 \times 10^9/l$: should this have been "white cell count"? If so, what was the differential? (3) In view of the above errors, was this a case report of a Hodgkin's or a non-Hodgkin's lymphoma as the title of the letter could be taken to imply Hodgkin's disease presenting with hypercalcaemia?

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- Ellis RD, Beck PR, Mondal BK. Hodgkin's disease presenting with hypercalcaemia. *J Clin Pathol* 1989;42:1228.

Dr Ellis comments:

I hope the following notes will clarify the points raised by Dr Luckit.