To the Editors:

Multiple autoimmune phenomena preceding a lymphoproliferative disorder

Autoimmune haemolytic anaemia (AIHA) is one of the commonest autoimmune phenomena recognised in association with lymphoproliferative disorders (LPDs). There have been only a few studies on subsequent development of LPDs in patients with autoimmune phenomena including AIHA [1, 2, 3].

A 28-year old Caucasian man presented with pallor, jaundice and splenomegaly. His haemoglobin was 83g/l, reticulocytes 13.2%, bilirubin 92 µmol/l, LDH 2718 U/l, haptoglobin <0.1 g/l (0.6-2.7) and direct antiglobulin (Coomb's) test was positive with IgG and C3d. A warm autoimmune haemolytic anaemia was diagnosed. The autoimmune screen including ANA was negative. His bone marrow showed intense erythroid hyperplasia with a small population of B cells expressing CD19, CD20 and CD22 but negative for CD5, CD10 and CD23. There was evidence of Kappa light chain restriction and an IgH gene rearrangement raising the possibility of an underlying lymphoproliferative disorder. However the trephine failed to confirm LPD.

Two years later he developed painful joints and vasculitic skin lesions. The autoimmune screen remained negative but lupus anticoagulant was detected.

He developed accelerated haemolysis and the repeat bone marrow study showed focal infiltration with small mature lymphocytes consistent with a B cell lymphoproliferative disorder. The spleen histology showed infiltration with small lymphocytes and immunophenotyping and histochemistry confirmed a B cell small lymphocytic lymphoma.

Six months later he presented with extensive superficial thrombophlebitis. At this time, antinuclear antibodies, β2 GP-1 IgG and low titres of anticardiolipin antibodies were detected. Secondary antiphospholipid syndrome was diagnosed.

Autoimmune manifestations in LPDs range from the presence of subclinical autoantibodies to the presence of well-defined autoimmune entities including autoimmune haemolytic anaemia (AIHA). In a study of 107 patients with AIHA, 19 (18%) developed LPDs within a median of 26.5 months and the majority were non-Hodgkin lymphomas (NHL) [4]. In this study, older age, presence of AIHA and serum monoclonal protein was identified as independent factors correlated with future development of LPD.

The pathogenesis of LPD developing later in the course of AIHA is not clear. The possibility of failure to recognise a developing lymphoproliferative process in early stages exists in many cases. Some propose that the defects in the anti-apoptotic gene or the loss of homeostatic mechanisms that prevent the over expansion of auto-reactive clone in some patients with AIHA may lead to subsequent development of lymphoid malignancies [7]. The alkylating agents and immunosuppressants used to treat AIHA may potentiate the subsequent development of LPDs.

The association of LPDs and SLE and antiphospholipid antibody syndrome has been noted. In one study relative risk for NHL in SLE patients was reported as high as 3.6 (n=5; 95%CI 1.2-8.6)[8].

Another study of sera of 90 consecutive unselected patients with NHL, 26.6% were found to have antiphospholipid antibodies [5]. There was no correlation between the disease severity with the antibody positivity.

There is evidence to justify a periodic evaluation of patients with AIHA for an underlying LPD and the presence of autoantibodies could be the first clue to the existence of underlying haematological malignancy.

References

1. Sallah S, Wan JY, Hanrahan LR. Future development of lymphoproliferative disorders in patients with autoimmune hemolytic anemia. *Clinical Cancer Research* 2001; 7: 791-4.
2. Polliak A, Lugassy G. Autoimmunity and auto-immune syndromes associated with and preceding the development of lymphoproliferative disorders. *Leukaemia* (Baltimore) 1992; **6**:152-4.
3. Oleinick A. Leukaemia or lymphoma occurring subsequent to an autoimmune disease. *Blood* 1967; **29**: 144-53.
4. Staus SE, Sneller E, Leanardo MJ, Puck JM, Straben W. An inherited disorder of lymphocyte apoptosis: the autoimmune lymphoproliferative syndrome. *Annals of Internal Medicine* 1999; **30**: 591-601.
5. Mellemkjaer L, Andersen V, Linet MS, Gridley G, Hoover R, Jorgen HO. Non-Hodgkin's lymphoma and other cancers among a cohort of patients with systemic lupus erythematosus. *Arthritis and Rheumatism* 1997; **40**: 761-8.
6. Genvresse I, Luftner D, Spath-Schwalbe E, Buttgereit F. Prevalence and clinical significance of anticardiolipin and antibeta2-glycoprotein-I antibodies in patients with non-Hodgkin's lymphoma. *European Journal of Haematology* 2002; **68**: 84-90.

Harindra Karunatilake (Registrar), and **Michael Elliott Pidcock** (Director), *Haematology Unit, The Canberra Hospital, Canberra, Australia.*
Correspondence: HK, *e-mail <sanyalharindra@yahoo.com>.* *Received 17 January, and revised version accepted 8 June 2007. Competing interests: none declared.*