Non-Hodgkin’s lymphoma in rheumatoid arthritis

Non-Hodgkin’s lymphomas are malignant tumours of B cells, T cells, or histiocytic cells, lacking the characteristic Reed-Sternberg cells seen in Hodgkin’s lymphomas. They may occur in either nodal or extranodal sites, and are characterised by lymphadenopathy, malaise, fever, weight loss, or anaemia.

Non-Hodgkin’s lymphoma has been reported in association with a number of autoimmune diseases, including Sjögren’s syndrome and rheumatoid arthritis (RA).

Studies of rheumatoid arthritis

A large population based study of 11 483 patients with RA in Finland found an excess of non-Hodgkin’s lymphomas, with an estimated 2.7 times greater relative risk, when compared with the rest of the population. A smaller hospital based cohort of 489 patients with RA in Birmingham, England found the relative risk was 26 times greater. Not all studies have confirmed an association between these two diseases, however, and large cohorts of patients with RA have been studied in which no cases of non-Hodgkin’s lymphoma were reported.

Possible reasons for the apparent discrepancies between these studies include, firstly, the methodology used in the study. Those studies using proportional mortality ratios probably do not show an increased incidence of non-Hodgkin’s lymphoma because there is still greater increase in deaths due to infective, cardiovascular, and respiratory causes that masks this effect. Secondly, non-Hodgkin’s lymphoma is an uncommon disease and its absence in some of the negative studies may be a type 2 error and be compatible with the degree of increased risk seen in the Finnish study. Finally, the Finnish study used a national insurance register of all cases of RA; however, this register included small numbers of patients with other connective tissue diseases and ankylosing spondylitis, and probably also included many cases of mild RA, in contrast with the Birmingham study. Therefore, possibly, the higher relative risk found in this smaller study reflects the incidence in a cohort of patients with more severe disease.

Sjögren’s syndrome

Kassan et al showed a much increased incidence of non-Hodgkin’s lymphoma in both primary and secondary Sjögren’s syndrome. Possibly, therefore, the association noted between RA and non-Hodgkin’s lymphoma is spurious and secondary to the presence of Sjögren’s syndrome in the patients with RA. The patients studied by Kassan were unusual, however, in that five out of seven of the cases of non-Hodgkin’s lymphoma occurred in patients treated with either radiotherapy or chemotherapy. The incidence of non-Hodgkin’s lymphoma in patients with Sjögren’s syndrome with milder disease not treated in this way has yet to be established. In the two largest series of non-Hodgkin’s lymphoma in patients with Sjögren’s syndrome was only 13% and 17%, though the diagnostic criteria used may mean that these figures are underestimates. Overall, the evidence suggests that there is an association between non-Hodgkin’s lymphoma and RA that is independent of the presence of Sjögren’s syndrome.

Aetiology and pathogenesis

Non-Hodgkin’s lymphoma might occur in patients with RA as a result of a genetic predisposition to both diseases. Alternatively, there might be a common environmental cause. There is little evidence to support such hypotheses, however, and interest has focused on the role of the RA disease process and of the treatment used in RA in the aetiology of non-Hodgkin’s lymphoma.

Natural killer cell activity may be important in immunosurveillance and host defence mechanisms against tumour formation. C57BL/6 mice have a specific defect in natural killer cell lysis of target cells; homozygote mice have an increased number and rate of growth of transplanted syngeneic leukaemias compared with phenotypically normal heterozygote litter mates. In humans there is reduced natural killer cell activity in patients with tumours and in normal subjects with a high family history of cancer. In RA reduced natural killer cell activity is found in synovial fluid and in whole blood (though this has not been confirmed in all studies), which may be related to RA disease activity. This would seem to be evidence for a defect in patients with RA that might lead to an increased risk of non-Hodgkin’s lymphoma. An increased incidence of all tumours has not been found in RA, however, and an increase in selected tumour types only is not predicted by a general immunosurveillance theory. The relevance of the animal studies and in vitro studies of natural killer cell activity to clinical production of tumours is not established.

Non-Hodgkin’s lymphoma occurs more commonly than expected in transplant recipients. Reduced cell mediated immunity, manifested by an impaired ability to control viral infection, may be important in the aetiology of non-Hodgkin’s lymphoma in both RA and transplant recipients.

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Leader
Epstein-Barr virus infects B cells which are prevented from proliferating by HLA restricted T cells. Epstein-Barr virus infection has been implicated in the aetiology of Burkitt's lymphoma and other lymphoproliferative disorders. In the X linked recessive lymphoproliferative syndrome Epstein-Barr virus infection results in an often fatal lymphoproliferative state. In transplant recipients such infection can lead to the development of lymphomatous tumours. The non-Hodgkin's lymphomas developing in transplant recipients (like most of those seen in RA) are B cell non-Hodgkin's lymphomas; most of them are polyclonal, however, and often respond to withdrawal of immunosuppression and antiviral treatment. It is not known if the non-Hodgkin's lymphoma seen in RA is monoclonal or polyclonal, and a comparison between such a lymphoma developing in transplant recipients and in RA may not be justified. In RA abnormal monocyte function impairs the ability of T cells to prevent proliferation of Epstein-Barr virus infected B cells. This is associated with reduced interleukin-2 and interferon gamma production. If Epstein-Barr virus infection has a role in the aetiology of some non-Hodgkin's lymphomas this would provide a theoretical explanation for the increased incidence of non-Hodgkin's lymphoma in RA.

It is likely that the use of immunosuppressive treatment in transplant recipients is implicated in the increased incidence of non-Hodgkin's lymphoma. There is concern that the increasing use of cytotoxic drugs in the control of RA may contribute to the association between non-Hodgkin's lymphoma and RA. The NZ/B1L mouse is a model for systemic lupus erythematosus, and has a high incidence of non-Hodgkin's lymphoma. This risk is increased further by treatment with azathioprine. In patients with Sjögren's syndrome reported by Kassen et al the incidence of non-Hodgkin's lymphoma was increased in all groups of patients, but was highest of all in the patients treated with cytotoxic drugs. Kinlen et al found an increased incidence of non-Hodgkin's lymphoma in patients with RA treated with cytotoxic drugs, with a relative risk 11 times greater than that for the general population. There was no control group of patients with RA not treated with cytotoxic drugs, however, and of the 50 patients with RA and non-Hodgkin's lymphoma reported in two other series, only two had been treated with such drugs. Retrospective studies of the incidence of non-Hodgkin's lymphoma in patients with RA treated with cytotoxic drugs compared with the incidence in control patients with RA have been conflicting. Some studies suggest that there is no risk of non-Hodgkin's lymphoma attached to the use of cytotoxic drugs in the doses used in RA, whereas others suggest a small additional risk. Silman et al found three cases of non-Hodgkin's lymphoma in 202 patients with RA treated with high dose azathioprine (median dose 300 mg/day) for a median of 35 months, followed up for 10 years. A fourth case occurred early in the study and might have been present before azathioprine treatment was started. This compared with two cases of non-Hodgkin's lymphoma occurring in a control cohort of patients with RA matched for age and year of diagnosis of RA. Overall, there is little compelling evidence to suggest a major risk of non-Hodgkin's lymphoma caused by cytotoxic drugs; studies of the safety term use of these drugs are still needed.

### Conclusion

Available evidence suggests that non-Hodgkin's lymphoma develops more commonly than expected in RA, though the precise relative risk is difficult to assess. This development is probably due principally to the RA disease process, rather than to the treatments used in patients with RA. Reduced cell mediated immunity, manifested as impaired host defence mechanisms against oncogenic viruses, or as reduced natural killer cell activity, may be important in the pathogenesis of non-Hodgkin's lymphoma.

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