Editorial

Malignancy and Rheumatic Disease — A Real Association?

Links between autoimmune rheumatic diseases (ARD) and malignancy go back 100 years: Stertz in 1916 reported the case of a patient who had inflammatory muscle disease and a gastric carcinoma[1].

During the past 30 years, there have been many attempts to determine more precisely the link between cancer and ARD. The best established connections are those between Sjögren's disease and non-Hodgkin's lymphoma (NHL)[2]; and adult onset dermatomyositis and a variety of solid tumors, notably ovarian, pulmonary, and pancreatic tumors[3-5]. More recently, a weak but definite link has been reported between systemic lupus erythematosus (SLE) and non-Hodgkin's lymphoma[6].

The explanation of this association between most ARD and cancer remains elusive. Given that both cancer and ARD are relatively common, the association may be due to chance alone. The possibility exists, however, that an ARD developing shortly after a diagnosis of cancer is in fact a paraneoplastic syndrome. Alternatively, the malignancy might be a consequence of immunosuppressive therapy often used in the treatment of patients with ARD[6].

Whereas this possible link to therapy is clearly a possibility in some cases, the recently published analysis of the patients with SLE indicated that the tumors occurred early, not late, in the course of the disease[6]. Further, as Sjögren's patients are rarely treated with immunosuppressives, no drug link can explain the connection with increased risk.

Several studies have, however, indicated an increased risk of lymphoproliferative malignancies in patients with rheumatoid arthritis (RA) that may well be related to the use of cytotoxic agents or prolonged immunosuppressive therapy[7,8]. Cases of lymphoma occurring in patients with RA receiving low-dose methotrexate therapy have been reported. In some cases, the lymphoproliferative disorders occurred in the context of associated Epstein-Barr virus infection, and tumor regression was noted to occur after discontinuation of methotrexate[9,10].

Additional studies are needed to define clearly the tumor-inducing role of immunosuppressive therapy, including the newer anti-tumor necrosis factor-α (TNF-α) agents, in patients with ARD. The definitive answer to the possible anti-TNF-α links to cancer should come from the biological register established by the British Society for Rheumatology. Four thousand patients with RA each taking one of the 3 approved anti-TNF-α drugs and 4000 patients with RA not taking any of these drugs are being followed in a longterm fashion.

As indicated above, it is well recognized that patients with malignancies may develop autoimmune and rheumatic manifestations. A new methodology called SEREX (serological analysis of recombinant cDNA expression libraries of human tumors with autologous serum) is adding significantly to our knowledge of autoantigens[11].

Several bona fide studies employing this technique list the role of tumor-associated autoantibodies against various tissue-specific antigens, membrane receptors, and nuclear proteins (including tumor suppression genes)[12]. Although still embryonic, such pioneering research may pave the way for a better understanding of autoimmunity, and facilitate early detection and treatment of malignancies.

It is of interest that non-Hodgkin's lymphoma (NHL) appears to be the commonest cancer link in several ARD. The article by Cuttner, *et al* in this volume of *The Journal* adds to our knowledge by reviewing this problem[13], but starting from the endpoint of malignancy and working backwards to identify those patients who had evidence of an autoimmune disease (AID). The authors have reviewed patients with known NHL, comparing them with patients who have other hematological disorders to determine the prevalence of associated AID.

The authors did not limit their analysis to patients with ARD, but also considered diseases such as inflammatory bowel disease and gluten enteropathy. The inclusion of uveitis may have been inappropriate, however, without fur-

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ther clarification of the etiology, as uveitis may be of non-autoimmune origin. It is also not clear what the relevant autoimmune tests for inflammatory bowel disease, polymyalgia rheumatica, polyarteritis nodosa, chronic urticaria, pemphigus, and psoriasis are. It would have been helpful to mention whether tissue (histological) confirmation of these diagnoses was used where appropriate in addition to clinical features and serological markers.

It is not entirely clear whether the onset of AID in patients with NHL was confirmed by chart review or whether the authors relied solely upon patient report. This doubt obscures the latency period between the diagnosis of AID and the development of NHL.

Further details about the control group would have benefited this study. The authors compared the NHL patients with those who had hematological disorders as well as "other patients." However, it is not stated what diseases constituted the group of "other patients," 43 in all. They noted that the NHL autoimmune patients were more likely to have had a prior rheumatologic disease, but the details were not clarified.

The authors observed an association between the use of immunosuppressive drugs in the NHL patients versus the controls. It is not clear at what stage these therapies were used, and whether the drugs such as MTX were used for treating the rheumatic disease or the malignancy. Such information would have strengthened any association between the two.

It is interesting to note their finding that the most frequent disorders in NHL patients were RA (n = 7) and autoimmune hypothyroidism (n = 7). Only 2 of the patients with NHL had Sjögren's and they both had Graves' disease.

Four of the patients with RA received immunosuppressives, which might have been a contributing factor. It is notable that the patients with autoimmune thyroid disease (n = 7) constitute the (equal) highest group with NHL. Since they were almost certainly not treated with immunosuppressive drugs and were also the groups most likely to have an IgG kappa monoclonal antibody, it is tempting to speculate that these patients may be at particular risk of developing neoplasia.

Cuttner and colleagues have succeeded in heightening the awareness of autoimmune disease and NHL in females (20% of all women with NHL compared to 7% of controls) ($p = 0.001$). They conclude that for patients of the same sex and age, patients with AID are 2.6 times more likely to have NHL than controls.

A dedicated attempt to study the link between cancer and AID is certainly a step in the right direction. Given the potential benefits of detecting early malignancies, such studies provide a platform for the development of age-specific screening guidelines for patients at high risk, and for the development of optimal management protocols for autoimmune diseases.

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