Association between azathioprine therapy and lymphoma in rheumatoid disease

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Summary

Three out of 41 patients treated with azathioprine and low-dose corticosteroids from 1976 to 1983 developed non-Hodgkin's lymphoma. This strikingly high incidence of lymphoma may be a reflection of long-term use of azathioprine.

Introduction

Although it is possible that there is an increased incidence of reticuloendothelial tumours in rheumatoid patients, controversy remains as to whether or not this is due to the disease process itself or to the therapy[1-3]. Prior[4] reported 6 cases of lymphoma in a consecutive series of 489 rheumatoid patients followed from 1964 to 1981; none of these patients had received azathioprine. Isomaki[5] reported a highly significant increase in the number of cases of leukaemia, lymphoma, Hodgkin's disease and myeloma in patients with rheumatoid disease in Finland, but no details of drug therapy were given.

Of 41 patients treated with azathioprine at King's College Hospital between 1976 and 1983, 3 developed non-Hodgkin's lymphoma. This represents a striking increase in the incidence of lymphoma and we wonder if long-term immunosuppression with azathioprine and corticosteroids has contributed to this in 2 of the patients. Much of the literature on the use of azathioprine in rheumatoid disease reports a much shorter period of follow up[1-3,6] and does not show any increase in reticuloendothelial tumours. It is possible that much longer follow up is needed to be more confident in this information, and it is perhaps salutary to recall the 20-year lag before the increased incidence of leukaemia in patients treated with radiotherapy for ankylosing spondylitis was appreciated[7].

Case reports

Case 1: A 61-year-old woman with a 20-year history of nodular seropositive rheumatoid arthritis had been treated with 50–150 mg azathioprine daily for 13 years after developing proteinuria on sodium aurothiomalate (Myocrisin). Her disease was well controlled and with surgery, including a total knee replacement, she was able to work full-time as a secretary.

Her blood count had been normal until August 1984 when she developed thrombocytopenia. The azathioprine was discontinued and she went on holiday. On her return she presented with a 10-day history of widespread palpable purpura and on examination the spleen was palpable 7 cm below the costal margin. She was now pancytopenic and hypogammaglobulinaemic. A marrow biopsy was essentially normal. Initial management was with high-dose steroids and vincristine. She developed a gastrointestinal bleed. Splenic ultrasound showed the spleen to have enlarged further to at least 25 cm below the costal margin. Immunofixation of her serum showed a lambda light chain, also present in the urine. The spleen was removed for diagnosis and treatment of her pancytopenia, the differential being between Felty's syndrome and a lymphoma of the spleen. She died postoperatively from septicaemia and acute renal failure.

The spleen measured 24 × 13 × 7 cm, and weighed 1.31 kg. Slicing revealed multiple yellow-white areas, measuring up to 4 cm in diameter. Histological examination showed diffuse infiltration of both red and white pulp by a malignant infiltrate including many large cells with well defined nuclear membranes, multiple nucleoli and ample cytoplasm. Immunostaining using the immunoperoxidase technique showed many of these cells to contain lambda light chains. The appearances were of high-grade non-Hodgkin's lymphoma of immunoblastic type. At post-mortem examination, there was no evidence of lymphoma in bone marrow, liver, lymph nodes or other tissue.

Case 2: A 58-year-old man, who had had nodular seropositive rheumatoid arthritis since the age of 16, developed a painless swelling in his right axilla in June 1983 associated with 6.3 kg weight loss. On examination he had enlarged lymph nodes in his axillae, cervical and inguinal regions. In the past he had had bilateral knee arthrodeses, a total hip replacement and a left girdlestone procedure.

From 1981 he had had one year's treatment with 150 mg azathioprine daily which was discontinued because of persistent nausea. He had previously developed neutropenia on Myocrisin and then proteinuria while on penicillamine. His mother had had radiotherapy 10 years previously for 'lumps in her groins', and is alive and well.

The patient's node was biopsied, and microscopical examination showed effacement of lymph node architecture and replacement of the node by an infiltrate of malignant cells characterized by large vesicular nuclei, many of which were indented, and showing prominent central nucleoli. Cytoplasm was ample, pale and eosinophilic. Immunostaining using the immunoperoxidase technique showed cytoplasmic alpha-1-antichymotrypsin. The appearances were of a histiocytic lymphoma.

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In August 1983 he was treated with one course of cyclophosphamide, adriamycin and vincristine. He refused further treatment.

Case 3: A 49-year-old housewife with a 15-year history of severe seropositive erosive rheumatoid arthritis had been treated initially with Myocrisin and prednisolone. During the first four years of her disease she developed severe damage to many of her joints and required a left total hip replacement in 1975. Penicillamine therapy was started but soon discontinued due to proteinuria, and from 1976 she was managed on azathioprine 100 mg daily, prednisolone 10 mg or less daily and various non-steroidal anti-inflammatory medications. On this treatment her full blood count was normal and her previously high ESR was usually in the normal range. She had a right total hip replacement in 1978 and in 1981 had two stress fractures of her lower tibiae. There was no Sjögren's syndrome and she was otherwise well.

In October 1984 she developed a painless swelling in the right parotid gland. A wedge biopsy was taken early in 1985 when the parotid swelling was enormously enlarged and there was displacement of the trachea with 7th and 12th nerve palsies. Microscopical examination showed extensively necrotic material, with several surviving islands of cells whose cytological features suggested high-grade non-Hodgkin's lymphoma of diffuse undifferentiated large cell type.

Due to her severe clinical state radiotherapy was started immediately and the tumour, which was dramatically radiosensitive, disappeared after 2000 centigrays of treatment. A CT scan showed splenomegaly but no secondary deposits and the bone marrow trephine was clear. She is currently under observation and has had no further treatment because of her frail clinical state.

Discussion

All 3 patients reported here suffered from severe, crippling rheumatoid disease which had not been satisfactorily treated with penicillamine or gold. All required corticosteroids in addition to azathioprine.

Case 1 was an interesting diagnostic problem, initially presenting with thrombocytopenia. From an extensive review of the literature, Whisnant and Pelkey[8] found a 4% incidence of this complication during drug trials. In our experience it is very unusual after prolonged therapy with azathioprine. The severe purpura was striking and, with the rapidly enlarging spleen, unusual for the presumptive diagnosis of Felty's syndrome[9]. The results of immunofixation of serum and urine, revealing a monoclonal gammopathy, were suggestive of a haematological malignancy which was confirmed at operation when a B-cell lymphoma of the spleen was diagnosed.

Case 2 developed histiocytic lymphoma 9 months after discontinuation of azathioprine. These lymphomas have, until recently, been infrequently reported in association with rheumatoid disease[10]. Another case of B-cell lymphoma occurred in Case 3 and interestingly there was no evidence of Sjögren's syndrome, which is known to be associated with an increased incidence of lymphomas[11]. On the other hand, azathioprine is known to produce a two-fold increase in chromosomal abnormalities in rheumatoid subjects[12]. Much of the concern regarding azathioprine therapy in rheumatoid disease has been in response to the markedly increased incidence of lymphomas, especially non-Hodgkin's type, in patients receiving renal transplants[13]. Here a predilection for central nervous system involvement is marked and the tumours appear after a short induction period.

In 2 of our patients the lymphomas appeared after many years therapy with azathioprine and corticosteroids, and if there really is an increased incidence of lymphoma in such patients it may be associated with a different pathological process.

It is only by a long-term prospective study of a substantial number of patients that the rate of malignancy in rheumatoid subjects treated with immunosuppressive therapy can really be determined. Such a study is under way in the United Kingdom and the results are awaited with great interest.

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