SUMMARY: A patient is described who developed a malignant lymphoma (immunoblastic sarcoma) within two years of the onset of rheumatoid arthritis. The possible pathogenesis of the lymphoma and its association with rheumatoid arthritis are discussed.

Introduction

Immunoblast was the name proposed by Dameshek in 1963 to describe an antigenically "switched on" or transformed lymphocyte. B and T immunoblasts develop when the corresponding small resting lymphocyte is stimulated. The B immunoblasts further mature into plasma cells and both have been shown to produce antibodies after antigen stimulation. Lukes and Collins, by correlating immunological function with microscopic appearance, proposed a classification of lymphomas in which they recognised a highly malignant tumour composed of proliferating immunoblasts. This they called immunoblastic sarcoma (IBS). Several of their patients gave a history of a chronic immune disorder, for example, rheumatoid arthritis or systemic lupus erythematosus. They suggested that an abnormal immune system in some way predisposed to the development of this lymphoma.

The classification and nomenclature of the non-Hodgkin's lymphomas is controversial. The Rappaport classification (Table I), based exclusively on morphology, includes a group of "histiocytic" lymphomas (reticulum cell sarcoma). However, when immunological methods are applied to these so-called histiocytic lymphomas, the majority are found to be tumours of transformed lymphocytes, most commonly of "B" cell lineage. True histiocytic lymphomas are rare. Reticulum cell sarcomas (or "histiocytic" lymphomas of Rappaport) have been reported in patients with Hashimoto's thyroiditis, Sjögren's syndrome, coeliac disease and renal transplant recipients, all conditions in which there is an abnormality of the immune system. As the majority of these tumours are derived from "B" lymphocytes and many of them closely resemble immunoblastic sarcoma it may be that IBS is more common than previously appreciated. Indeed, Lukes and Tindle have suggested that "reticulum cell sarcomas" arising from transplant patients are in fact examples of IBS. A patient is described who developed IBS within a short time of the onset of rheumatoid arthritis.

Case history

A caucasian male, aged 66 years, was admitted to hospital in October 1976 with chest pain suggestive of myocardial ischaemia. Cardiac enzymes were
Table I

Non-Hodgkin's lymphomas — proposed classification

<table>
<thead>
<tr>
<th>RAPPAPORT$^3$</th>
<th>Class</th>
<th>LUKES and COLLINS$^4$</th>
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<tbody>
<tr>
<td>Lymphocytic, well differentiated</td>
<td>I Undefined cell type</td>
<td></td>
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<tr>
<td>Lymphocytic, poorly differentiated</td>
<td>II T-cell types</td>
<td>1. Mycosis fungoides and</td>
</tr>
<tr>
<td>Mixed (histiocytic—lymphocytic)</td>
<td></td>
<td>2. Convoluted lymphocytic</td>
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<tr>
<td>Histiocytic (Reticulum cell sarcoma)</td>
<td>III B-cell types</td>
<td>3. ? Immunoblastic sarcoma</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td></td>
<td>(of T-cells)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. ? Hodgkin's disease</td>
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<tr>
<td>(In addition to cytological characteristics the lymphomas are designated nodular or diffuse)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV Histiocytic types</td>
<td>V Unclassifiable</td>
<td></td>
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</table>

raised and serial ECG's showed ST segment and T wave changes consistent with the clinical diagnosis of cardiac ischaemia. Recovery and mobilisation were rapid and complete. At follow-up 18 months later a chest X-ray revealed bilateral small pleural effusions. Review of chest X-rays since discharge from hospital showed changes which were interpreted as showing pericardial effusion with later resolution. A test for rheumatoid factor (RA latex) was positive at a titre of 1:1024. Antinuclear antibodies were also present, however, anti-double strand DNA antibodies were not found. A retrospective diagnosis of rheumatoid serositis affecting pleura and pericardium was made. At this time he was asymptomatic.

In June 1978 pain and morning stiffness developed in the small joints of the hand. X-rays showed bony erosions at the metacarpophalangeal joints and the ulnar styloid. Symptoms responded well to soluble aspirin.

Five months later he was admitted for investigation of weight loss, cervical and axillary lymphadenopathy. Investigations revealed a mild normochromic anaemia and an ESR of 70 mm in the first hour. The RA latex was again positive. Plasma albumen was reduced at 31 gm/l. Immunoglobulins were normal.

Microscopical examination of an excised lymph node demonstrated complete effacement of its architecture by a diffuse polymorphous cellular infiltrate. Thin resin sections showed predominantly large lymphoid-type cells with prominent central nucleoli (Fig 1). The cell cytoplasm was intensely pyroninophilic. The presence of such cells in large numbers warranted a diagnosis of malignant lymphoma, immunoblastic type (immunoblastic sarcoma). Unfortunately corroborative surface marker studies could not be performed and immunoperoxidase studies of the immunoglobulin content of the cells were equivocal. The prognosis was thought to be poor.
Immunoblastic Sarcoma and Rheumatoid Arthritis

Fig. 1. Diffuse infiltrate of large lymphoid cells with irregular nuclear outline, margined chromatin and prominent nucleolus. (Resin section, toluidine blue stain. Original magnification x 500)

Pulsed chemotherapy with cyclophosphamide, vincristine and prednisolone produced some tumour shrinkage, but gradually cervical nodes began to enlarge and his condition deteriorated despite continued chemotherapy. Klebsiella pneumonia developed and he died six months after the diagnosis of immunoblastic sarcoma.

At autopsy, dense fibrosis obliterated the pleural and pericardial cavities. All major lymph node groups were involved by immunoblastic malignant lymphoma and there were discrete tumour metastases in brain, lungs, kidneys, liver and spleen. The synovium showed microscopic inflammatory changes consistent with rheumatoid arthritis.

Comment

Many different classifications of the non-Hodgkin's lymphomas exist, due in part to the acquisition of new knowledge and evolving concepts of lymphoid function. To date however, no classification has been universally accepted.

The Rappaport classification is based on architecture of the involved lymph nodes and cytology of the malignant cells. "Histiocytic" lymphomas (reticulum cell sarcoma) of Rappaport, form a heterogenous group. Recent data has shown that true histiocytic lymphomas are rare and that most of Rappaport's "histiocytic" tumours are in fact composed of transformed lymphocytes. Unfortunately Rappaport's choice of terms was made in 1956 and 1966 when large lymphoid cells were designated as histiocytes. This approach is not accepted as scientific today.
Lukes and Collins\(^4\) used immunological parameters to subdivide lymphomas and attempted to interpret morphology in terms of immunological function. Included in their classification is the “B” cell immunoblastic sarcoma “morphologically characterized by a large amount of pyroninophilic cytoplasm and a large nucleus which is commonly oval in shape, has a pale staining chromatin and usually two or three nucleoli similar to the large non-cleaved follicular central cell”. Evidence of rapid growth is usually present with tissue necrosis and increased mitotic activity. Prognosis is poor with survival measured in months from diagnosis. Strauchen \textit{et al}\(^{13}\) re-examined a series of diffuse “histiocytic” lymphomas (under the Rappaport classification) using criteria partially based on Lukes and Collins’ concepts. In 66 cases examined, 13 were found to be pleomorphic pyroninophilic lymphomas consistent with immunoblastic sarcoma.

Examination of IBS under the electron microscope\(^{14}\) reveals many cytoplasmic polysomes, the organelles concerned with protein (antibody) synthesis. Cellular export mechanisms (endoplasmic reticulum and Golgi apparatus), however are not well developed, suggesting some degree of cytoplasmic “constipation”. When plasmacytoid features are seen with the light microscope in some tumours, the electron microscope shows dilated rough endoplasmic reticulum and a Golgi complex corresponding to the light microscope paranuclear “hof”. These findings suggests a range of differentiation and a developing cellular export capability. Indeed, monoclonal immunoglobulins have been found in a number of such patients. Many patients however have a diffuse polyclonal hyperglobulinaemia\(^{15}\).

Several conditions have been associated with the development of IBS; rheumatoid arthritis, systemic lupus erythematosus, Sjøgrens syndrome. Each of these is thought to involve chronic antigenic exposure or an abnormality of antigen recognition. Failure to eliminate antigen completely results in chronic immune stimulation with expansion of lymphoreticular tissue. Reactive lymphoid hyperplasia with lymphadenopathy is well recognised in rheumatoid arthritis\(^{18}\). Against this background, the development of a malignant lymphoma could be explained by Salmon and Seligman’s\(^{17}\) “two hit” hypothesis. Chronic antigen stimulation (the “antigenic event”) producing fertile soil for a mutagenic stimulus or “oncogenic event”, transforming a susceptible sub-population of cells into a malignant clone. Indeed lymph nodes showing only partial involvement by IBS often also show evidence of antigenic stimulation\(^{12}\). Recent study of lymphocyte sub-populations has shown that cells which in some way control and modify the immune response (suppressor lymphocytes) are reduced during active autoimmune disease\(^{18}\).

An unusual feature of the case described is the short time interval between the development of rheumatoid arthritis and IBS. In previous reports rheumatoid arthritis has been present for many years. Rheumatic symptoms can occasionally be caused by the presence of a malignant lymphoma (? tumour derived immune complexes). It has been shown however that in these cases lymphoma involvement is extensive\(^{19}\). It is unlikely therefore that the presenting symptoms in our patient were the result of a clinical occult lymphoma.

The rapid course seen in our patient is typical of immunoblastic sarcoma, death occurring within months of the diagnosis, despite aggressive chemotherapy.
Acknowledgements

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REFERENCES