Case report

Sjögren's syndrome and fibrosing alveolitis complicated by pulmonary lymphoma

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SUMMARY The case of a middle aged woman who presented with fibrosing alveolitis, in her mid-forties, followed by a sicca syndrome and who subsequently developed a pulmonary lymphoma (B cell) while receiving azathioprine therapy is recorded. Of interest was the absence of polyclonal B cell activation, e.g., production of rheumatoid factor, hypergammaglobulinaemia, high titre antinuclear antibodies or antibodies to extractable nuclear antigens (ENA) during most of her illness. Persistently raised IgM levels and low IgA levels were demonstrated. The relevance of azathioprine to development of the lymphoma is discussed.

Key words: sicca syndrome, azathioprine.

Case report

HISTORY AND EXAMINATION

This 59 year old woman first became ill at the age of 33 when she complained of polyarthralgias affecting the hands, knees, and ankles. Several years later at age 44, when admitted for a hysterectomy, a routine chest x ray showed reticular shadowing at the left base. She had a positive antinuclear factor (1/40), an increase of IgG and IgM globulin fractions, and autoantibodies were negative. A presumptive diagnosis of early fibrosing alveolitis was made. The following year she complained of recurrent 'gritty' eyes and attacks of conjunctivitis, and at the age of 50, when she presented herself as a blood donor, she was found to have a positive Coombs' test and the antinuclear factor was still 1/40. In 1979 she was found to have a positive Schirmer's test, and keratoconjunctivitis sicca was diagnosed. A salivary gland biopsy showed local chronic inflammation, atrophy of gland acini, and hyperplasia of the duct epithelium confirming Sjögren's syndrome. Because

of a raised erythrocyte sedimentation rate (ESR) of 155 m/h, a rash on the butterfly area of the face, and positive DNA binding she was thought to have systemic lupus erythematosus (SLE) in 1980, and treatment was started with systemic steroid therapy—prednisolone (40 mg daily) and azathioprine (150 mg daily). The rash was diagnosed as acne rosacea and responded to tetracycline therapy. Over the next year she developed multiple drug allergies (penicillin, nitrofurantoin, sulphonamides, tetracyclines, and lincomycin), a chronic watery diarrhoea, and recurrent upper respiratory infections. Over the ensuing five years she had a persistent chronic cough and required repeated hospital admissions, three of which were to the intensive care unit for treatment of these pulmonary infections. The offending organism was usually *Haemophilus influenzae*, but on one occasion (in 1985) she was found to have Epstein-Barr virus in the lungs. Her ESR remained persistently raised, and she was maintained on varying doses of prednisolone and azathioprine during this period.

Dyspnoea on exertion became a problem and by 1986 her exercise tolerance was reduced to 50 yards. From 1979 onwards her chest x rays were abnormal,

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showing persistent reticular shadowing at the bases with right middle lobe consolidation, later progressing to patchy, ill defined shadowing throughout both lung fields (Fig. 1).

In 1986 she was admitted to St Thomas's Hospital for evaluation and open lung biopsy. On admission she was Cushingoid, with a 'buffalo hump' and moon face. She complained of proximal weakness, dryness of the eyes and mouth, and felt generally unwell.

A mild synovitis of the small joints of both hands was present. Bilateral basal crepitations were audible, but the rest of the clinical examination was essentially normal.

INVESTIGATIONS

Investigations showed a normal haemoglobin, white cell and platelet count. Polyethylene glycol immune complexes were present to a level of 70 mg IgG/l (normal <49 mg IgG/l).

A complement screen was within normal limits. Antinuclear antibodies and organ specific antibodies (to thyroid, smooth muscle, mitochondria, and gastric parietal cells) were now negative. The latex and Rose-Waaler tests for rheumatoid factor were negative, as was the Coombs' test and the Venereal Disease Research Laboratory test.

Antibodies to double stranded deoxyribonucleic acid were persistently negative as were antibodies to extractable nuclear antigens (ENA).

The IgM concentration was persistently raised at 4.8 g/l (normal 0.5–2.0 g/l). The Schirmer's test was dry bilaterally.

Biopsy of minor salivary glands on this occasion did not show any abnormality and a radioactive pertechnetate scan of the parotid and submandibular glands did not show any abnormalities of secretory flow despite the subjective complains of xerostomia.

At operation the findings were of nodular infiltration of the middle and lower lobes, the middle lobe being completely solid with hard nodules present throughout the lung parenchyma.

Microscopy of the pathological specimens showed a fairly monomorphic infiltration by lymphoid cells (Fig. 2). In a solid nodule the alveolar structure was totally destroyed and was replaced by a diffuse sheet of cells, and at the periphery of the nodule the cells had infiltrated the interalveolar septa. The pleura and the walls of bronchi and of blood cells were extensively infiltrated. The cells were lymphoid in nature, larger than small lymphocytes, and there were many plasmacytoid cells and numerous large cells with fairly abundant cytoplasm and large vesicular nuclei with prominent nucleoli. Mitoses were fairly frequent. There were no follicles. In the solid area there was abundant eosinophilic material

Fig. 1a

Fig. 1b

Fig. 1c

Fig. 1 (a) Reticular shadowing at both bases, right middle lobe consolidation. (b) Follow up (two years later). Small opacities in both lower zones, basal reticular shadowing persists. (c) Four years later. Multiple opacities throughout both lung fields.

Fig. 2a

Fig. 2b

Fig. 2 (a) Lung and pleura showing destruction of alveolar structure and diffuse replacement by lymphoid cells. Note absence of lymphoid follicles. (b) Lung. Diffuse replacement by primitive lymphoid cells with large vesicular nuclei and prominent nucleoli.

which appeared to be organising fibrin and hyalinised collagen. There was no amyloid deposition seen, but fairly frequent giant cell granulomata were visible. No organisms could be identified. Immunohistochemistry showed the presence of intracellular IgM, and the cells stained monotypically for κ light chains. These appearances were interpreted as those of a B cell malignant lymphoma.

Discussion

This patient presented the unusual combination of several connective tissue diseases developed over a period of 20 years from age 33. She commenced with

an undiagnosed polyarthritis, followed 11 years later by presumptive fibrosing alveolitis (not proved by biopsy). Sjögren's syndrome, then possible SLE, and eventually developed a lymphoma of the lung. Although she had a positive salivary gland biopsy in 1979/80 combined with defective tear production (Schirmer's test) and diagnosed keratoconjunctivitis sicca, a repeat biopsy in 1986 was not abnormal nor was there any objective evidence of salivary gland malfunction by radioisotope scanning. There was never any evidence of B cell hyperactivity such as polyclonal hypergammaglobulinaemia or positive rheumatoid factor test, though IgM globulin levels were raised for several years, with a minimal increase of IgG noted at the age of 44.

The fibrosing alveolitis combined with the sicca syndrome were presumably responsible for the repeated and severe respiratory tract infections which necessitated so many hospital admissions. The reasons for the normal repeat salivary gland biopsy and testing in 1986 are unclear. At this time, apart from several years of corticosteroid and immunosuppressive therapy, the patient had also received several months of chlorambucil treatment for the lymphoma but still persisted with her subjective complaints of dry eyes and mouth, used hypromellose drops frequently and still demonstrated a positive Schirmer's test. Whether, in fact, because of the often 'patchy' involvement of salivary glands, a normal area was biopsied or whether the immunosuppression and other cytotoxic therapy had effected an alteration in gland morphology is open to conjecture.

First reported by Talal and Bunim in 1964,¹ over 100 cases of the association of a variety of lymphoid abnormalities with Sjögren's syndrome (SS) have now been seen. This lymphoproliferation has varied from 'pseudolymphoma' to overt lymphoma and has involved the lungs, kidney, gastrointestinal tract, or has been generalised. The course of the lymphoproliferative process has been seen to progress from a benign and polyclonal lesion to an overt monoclonal malignancy.²⁻³ Most patients with this complication have been shown to have monoclonal B cell neoplasms and have demonstrated IgM κ light chains,^{4,5} though T cell proliferation⁶ and IgM λ light chains have also been recorded.³

Primary (Waldenström's) macroglobulinaemia and a significant increase of IgM globulins were seen in the series of eight patients recorded by Talal *et al* in 1967.⁷ In addition to reticulum cell sarcoma,⁸ other histological varieties termed 'angioimmunoblastic', lymphadenopathy, and 'immunoblastic sarcoma' have also been described. This last term has been used recently to reclassify some of these neoplasms, and this type has been found to be

associated with autoimmune disease in approximately 30% of cases.^{9 10} It appears that previous descriptions of lymphomas associated with SS and termed reticulum cell sarcoma, histocytic lymphoma, and poorly differentiated lymphocytic lymphoma will all be now reclassified as immunoblastic sarcomata.

Recurrent parotid swelling, splenomegaly, and lymphadenopathy appear to confer a high risk for the subsequent development of malignancy in patients with SS,¹¹ and a drop in rheumatoid factor titre and IgM concentration may presage the appearance of this malignancy.¹ There is also some speculation as to whether this association is limited to those patients demonstrating anti-Ro antibodies.¹²

Initially, isolated benign lymphoepithelial proliferation (now termed myoepithelial sialadenitis) may occur in the salivary glands themselves, or serum autoantibodies may be present in otherwise asymptomatic patients. This situation may progress into frank SS with monoclonal immunoglobulin production and the appearance of 'pseudolymphomas'—a term used when immature, but seemingly non-malignant mononuclear cells infiltrate extraglandular tissue. The final stage occurs in a small percentage of patients when these lymphocytes undergo malignant transformation with possible accompanying hypogammaglobulinaemia and immunodeficiency. This has been likened by Talal to the relationship between benign monoclonal spikes and myeloma/macroglobulinaemia or between ARC (AIDS related complex) and AIDS (acquired immune deficiency syndrome).¹³

This progression from an autoimmune process to a lymphoma may be seen in spontaneous autoimmune disease, in mice with experimentally induced chronic graft versus host disease, and in patients with rheumatoid arthritis, where a recent study showed a 2.2% incidence of lymphoproliferative malignancies developing after a mean interval of 11.8 years.¹⁴

The lung is frequently involved in cases of generalised malignant lymphoma, and a primary tumour may be confused with, and must be differentiated from, localised inflammatory masses composed of lymphoid cells. In contrast with inflammatory masses, however, lymphomas are monomorphic and follicles with germinal centres are absent. The cells may invade the pleura, bronchi, and veins, but demonstration of monotypic neoplastic lymphoid cells by immunological marker studies confirmed the diagnosis in our patient.

The development of lymphoma may be related to either the sicca syndrome or to the possible effects of immunosuppressive therapy, and it is not possible

to establish clearly the definitive aetiology as this complication has been reported in all these circumstances.

SLE itself complicated by lymphoma has been recorded by Green *et al.*,¹⁵ who also referred to previous reports of a further 14 cases, most of which were non-Hodgkin's lymphoma and followed the diagnosis of SLE by two months to 12 years. There have also been other reports of lymphoma in SLE¹⁶⁻¹⁸ and in mixed connective tissue disease.¹⁹

Most of the published work recording the association of azathioprine with cancer has been in relation to transplant patients and includes 150 lymphomas in addition to other malignancies.

There have, however, been a substantial number of cases of malignancy in non-transplant patients treated with azathioprine, including not only SLE, but also idiopathic thrombocytopenic purpura, dermatomyositis, and rheumatoid arthritis in addition to sicca syndrome itself, and it appears that conditions associated with immunodeficiency lead to a higher incidence of lymphomas and leukaemias,^{20 21} particularly Sjögren's syndrome.¹¹

A multicentre trial presently being conducted has so far shown five patients treated with azathioprine who developed lymphoma, four with rheumatoid arthritis and one with SLE. The patients had received the drug for a period of time ranging from six to 156 months and the dosage varied from 50 mg to 200 mg daily (A Kay, personal communication).

Cyclophosphamide rather than azathioprine appears to be more particularly associated with an increased risk of lymphoproliferative malignancies especially in the renal transplant group.²² It has been suggested by some authors that the risk in rheumatoid arthritis is independent of previous immunosuppression²³ and that any additional risk attributable to these agents, although definite, is small (A D Steinberg, personal communication).

The role of the Epstein-Barr (EB) virus in the malignant transformation of primed lymphoid cells has been suggested.²⁴ Recent evidence for this hypothesis is found, for example, in post-transplant lymphomas, which showed the presence of EB virus nuclear antigen in all constituent cells^{25 26}; the subject has been well summarised by Hanto *et al.*²⁶ The study of oncogenes in such patients may in the future yield clues about the underlying pathogenesis.²⁷

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