Remission of scleroderma during chemotherapy for lymphoma

Marie Comer, Andrew R Harvey

Abstract
Temporary remission of scleroderma during the successful treatment of an associated malignant lymphoma by chemotherapy is reported in a patient with systemic sclerosis and mixed connective tissue disease. There is a well established relation between malignant disease and polymyositis/dermatomyositis but no overall association with systemic sclerosis or mixed connective tissue disease. Reports of the coexistence of malignancy and systemic sclerosis, however, emphasise a close temporal relation in their occurrence. A review of published work has identified several postulated mechanisms for this relation which may explain the response to chemotherapy.


A 31 year old previously healthy woman presented in May 1988 with sclerodactyly, intermittent arthralgia, weight loss of two stone in six months, Raynaud’s phenomenon, hoarseness, and self limiting diarrhoea. She had previously had two miscarriages. Investigation on initial presentation showed a strongly positive test for antinuclear antibodies (>800 IU speckled pattern) and an erythrocyte sedimentation rate (ESR) of 76 mm/hour. Other investigations, including a full blood count, urea and electrolyte profile, and DNA binding, were normal.

A year later she noted an enlargement of the lymph nodes in her neck. A biopsy sample showed nodular sclerosing Hodgkin’s disease of mixed cellularity with focal lymphocytic depletion. A thoracic computed tomography scan showed mediastinal lymphadenopathy and as systemic symptoms were present a clinical diagnosis of grade IIb Hodgkin’s lymphoma was made.

Chemotherapy was begun with the standard MOPP regimen (chlorambucil 10 mg daily day 1–10, procarbazine 150 mg daily day 1–10, prednisolone 40 mg daily day 1–14, vincristine 2 mg day 1, 2 mg day 8). Six courses were given between June and November 1989. By December 1989 there was considerable objective improvement in the sclerodermatous skin disease. The patient said that the scleroderma began to regress within four weeks of her first chemotherapy session. A bone marrow sample in January 1990 and a repeat mediastinal computed tomography scan showed no residual disease.

In March and April 1990 she was readmitted with pneumonia and abdominal pain respectively. On neither occasion was there clinical evidence of lymphoma and the scleroderma was still in remission. She did have increasing hoarseness of her voice, though an ear, nose, and throat assessment showed no abnormality.

She remained well until August 1990 when myalgia, arthralgia, fatigue, vomiting, dyspnoea on exertion, weight loss of four stones over two months, and amenorrhoea were the presenting features. Signs of scleroderma returned and extended rapidly to affect her proximal limbs and trunk. The severe vomiting was due to small bowel disease with systemic sclerosis confirmed endoscopically and radiologically, with no evidence of intestinal lymphoma. Investigation showed an increased serum creatinine kinase level (2445 IU/ml). An open muscle biopsy sample taken from the left quadriceps muscle showed muscle fibre regeneration but no inflammatory cell infiltrate. Other abnormal results included an ESR of 75 mm/hour, a restrictive pattern on pulmonary function testing, the presence of a λκ monoclonal paraprotein band, and a positive test for ribonucleoprotein antibodies. Her full blood count, urea, and electrolyte profile, and other autoantibody tests remained normal. The lupus anticoagulant (anticardiolipin antibody) test was negative.

Treatment was begun with prednisolone by mouth (60 mg daily) and cisapride with improvement in muscle strength and vomiting respectively. Six days after beginning treatment progressive thrombocytopenia occurred and cisapride was stopped. Over 16 days the platelet count continued to decrease further from an initial platelet count of 422 × 10^9/l to 48 × 10^9/l. There was no intravascular coagulopathy and she was receiving no drugs associated with thrombocytopenia. Sixteen days after the onset of the decline in the platelet count she had a sudden circulatory collapse associated with chest pain and dyspnoea. The electrocardiogram showed the acute development of a right bundle branch block and a sinus bradycardia progressing to asystole from which resuscitation was unsuccessful.

At necropsy there was no evidence of pulmonary embolism, myocardial infarction, nor a cerebral vascular event. Detailed cardiac dissection showed that the left branch of the bundle of His was interrupted. The right branch could not be identified. There was no macroscopic evidence of recurrent lymphoma. Pulmonary fibrosis was noted and the gastrointestinal tract showed changes of pneumatosis cystoides intestinalis, one of the less common gastrointestinal manifestations of systemic sclerosis.
Discussion

This case shows the regression of scleroderma following chemotherapy with the MOPP regimen and its recurrence at a time when subclinical lymphoma recurrence was possible as indicated by the presence of the monoclonal paraprotein band. We postulate a pathogenic relation explaining the coexistence of these diseases and their simultaneous resolution and recurrence. We also explore putative links between the development of scleroderma in a patient with pre-existing malignant disease, and conversely between tumour development in a patient with pre-existing connective tissue disease.

Previously published papers do not indicate a significant overall excess of malignancy in systemic sclerosis.\(^1\) There is, however, an increased incidence of neoplasia in many diseases in which tissue is subjected to persistent proliferation and repair. In patients with oesophageal carcinoma in systemic sclerosis malignant change develops in tissue affected by longstanding oesophageal disease.\(^2\)

There is an increased incidence of systemic sclerosis in patients with lung carcinoma, some series showing a preponderance of adenocarcinoma, a histological type characteristically found in scar tissue,\(^2\) and some series showing at least 50% to be alveolar cell carcinoma, a rare histological type.\(^3\) A study by Peters-Golden et al\(^4\) indicates that this relative increase of lung carcinoma in patients with systemic sclerosis is similar to that in idiopathic pulmonary fibrosis.\(^3\) Postulated explanations for this sequence of events include a sustained increase in mitotic activity in cells involved in the inflammatory component of the disease and those involved in tissue repair, impaired clearance of carcinogens in tissue with a disorganised architecture, and increased susceptibility to the secretion of inflammatory mediators by the cells which populate, for example, the alveoli in interstitial lung fibrosis.\(^3\)

Despite there being no known pathogenic link between the coincidence of neoplasia and systemic sclerosis except that accounted for in scarred tissues, reports of the two disease entities in coexistence stress a close temporal relation, suggesting that in some patients the presence of one disease may be implicated in the subsequent development of the second or may influence the behaviour of the second pathology. A close temporal relation between scleroderma and breast carcinoma has been cited by Forbes et al\(^5\) and supported in a study by Rounm and Medsger.\(^4\) Duncan and Winkelman\(^6\) observed regression of scleroderma in two patients treated for malignancy of the breast and bladder respectively. Lee et al\(^6\) reported simultaneous deterioration of scleroderma in a patient with primary breast cancer who developed metastatic disease.

Reports of cancer in mixed connective tissue disease are rare. Black et al\(^7\) reported a series of 40 patients with mixed connective tissue disease in which four developed a carcinoma. Bennett and O'Connell\(^8\) reported two cases of carcinoma in 20 patients with mixed connective tissue disease. Two studies with such small numbers in the context of a rare disease are insufficient to support any significant relation between carcinoma and mixed connective tissue disease. Lymphadenopathy has been reported to be present in 39–68% of patients with mixed connective tissue disease. Despite this we found only two reports of lymphoma and coexistent mixed connective tissue disease. The first was that of Frayha et al\(^9\) of a patient with mixed connective tissue disease, abdominal lymphoma, and Sjögren's syndrome. An association between Sjögren's syndrome and lymphoma is well documented but these workers propose that antibodies to Ro in mixed connective tissue disease may give a higher risk of lymphoma. Our patient did not have antibodies to Ro. The second report by McLeish et al\(^10\) was of a patient with non-Hodgkin's lymphoma and membranous nephropathy in mixed connective tissue disease.

One proposed mechanism for the temporal association of malignancy and systemic sclerosis/mixed connective tissue disease is of a pre-existing tumour inducing systemic sclerosis by the elaboration of a substance which may act at a distance on the skin provoking sclerodermatous change, or on other tissues to produce the systemic features of the disease. Such a substance may be a paraprotein or an autoantibody.\(^11\) The metabolite of the carcinoid syndrome (5-hydroxytryptamine) may induce sclerodermatous skin changes but not systemic disease.\(^12\) Weiner has reported the presence of the Scl 70 antibody relating to the development of malignancy.\(^13\) We postulate that a humoral or cell mediated immune process initiated by the lymphoma was responsible for the development of systemic sclerosis in our patient, and that this case suggests the possibility of identifying patients with systemic sclerosis amenable to immunotherapy and monitoring of their response using serological markers of the immune process.

Pre-existing scleroderma may be complicated by malignancy as a secondary event. Postulated explanations for this sequence of events are the same as those described here for the development of lung tumours.

The third possibility is of a common pathogenesis. A common genetic susceptibility has been considered by Forbes et al\(^1\) and Lee et al,\(^6\) though the numbers were small and the evidence anecdotal. It has been proposed that impaired immune regulation leading to uncontrolled lymphoid proliferation may predispose to the development of malignant lymphoma.\(^10\) An impairment of immune regulation with decreased circulating T cells and decreased suppressor cell function has been described in mixed connective tissue disease.\(^14\) Systemic sclerosis is known to occur in graft versus host disease.\(^15\) This illustrates the coexistence of systemic sclerosis and an abnormal cell mediated immune response inferring that an underlying derangement of immune regulation may occur and be common to the development of systemic sclerosis and the tumour.

We must also consider that the regression of the scleroderma may have been the result of treatment with the MOPP chemotherapeutic
regimen. High doses of steroids have been used in patients with systemic sclerosis with myositis, serositis, the oedematous phase of skin disease, and refractory arthritis with some degree of success, but such treatment generally requires a higher daily dose of prednisolone taken for a longer time than the prednisolone component of the MOPP regimen. Reports of the efficacy of chlorambucil in the treatment of systemic sclerosis have been conflicting.16 Vincristine, procarbazine, and combination chemotherapy have not been assessed as potential treatments for systemic sclerosis but such toxic drugs would carry a risk and morbidity that would probably limit their use to a life threatening situation.

Conclusions
We have reported the case of a patient whose initial presentation was that of systemic sclerosis but who went on to develop a grade IIb nodular sclerosing Hodgkin’s lymphoma. Following combination chemotherapy the tumour regressed completely followed by objective and subjective regression of the scleroderma. A year later features of systemic sclerosis recurred, this time in association with myositis and a positive test for antibodies to ribonucleoprotein. Rapid disease progression ensued and the appearance of a paraprotein band was noted suggesting subclinical lymphoma recurrence. A review of published work has shown that although there is no overall increase of carcinoma in patients with systemic sclerosis, when the two occur together a close temporal relation has been noted which suggests that one disease may influence the development or behaviour of the second. We postulate that a humoral or cell mediated immune process initiated by the lymphoma was responsible for the development of systemic sclerosis in our patient and we have speculated on the mechanisms by which tumour and connective tissue disease development and regression may interrelate.