Scleroderma in a child after chemotherapy for cancer

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ABSTRACT

The association of malignancy with scleroderma is very rare in childhood. A 13-year-old girl was diagnosed as having thymic carcinoma and received systemic chemotherapy. She presented with symptoms of Raynaud's phenomenon 9 months after the cessation of chemotherapy. She also had difficulty in swallowing. Based on the presence of Raynaud's phenomenon, characteristic skin changes over the face and hands, oesophageal involvement and pulmonary restrictive defect demonstrated by pulmonary function tests, the diagnosis of generalised scleroderma was established. There was no evidence of tumor recurrence. Although she was treated with penicillamine and prednisolone, no significant improvement was achieved in her condition during the 14-month follow up.

Introduction

It is widely accepted that there is a strong association between malignancy and collagen diseases such as dermatomyositis, systemic lupus erythematosus, and scleroderma (1-3). A link between scleroderma and cancer in adults has been less frequently reported than the association of dermatomyositis and cancer. There is no report addressing the association between scleroderma and cancer in the pediatric age group.

Here we report the development of scleroderma in a young female patient who received combined chemotherapy for the treatment of thymic carcinoma.

Case report

A 13-year-old girl had been admitted to a local hospital with the complaints of fatigue, anorexia and enlargement of the left cervical lymph nodes for the last six months. Biopsy findings from a lymph node were consistent with a metastatic carcinoma. After the diagnosis of malignancy, she was referred to our hospital for further evaluation and treatment. Investigations for possible primary origins were performed. Computerized tomography of the thorax revealed sternal, pre-vascular lymphadenopathies and an anterior mediastinal mass. Since immunohistochemical staining of the specimen from the cervical lymph node was also positive for epithelial membrane antigen, the tumor was determined to be of thymic origin. The work-up of other possible primary origins was negative.

The patient was treated with systemic chemotherapy consisting of vincristine 1.4 mg/m^2 on day 1, cisplatin 90 mg/m^2 on day 1, doxorubicin 30 mg/m^2 on days 1 and 2, and cyclophosphamide 10 mg/kg on days 1 through 3 intravenously, repeated every three weeks for four cycles. Subsequently maintenance therapy including cisplatin, dacarbazine, actinomycin-D and cyclophosphamide was initiated. Since no tumor recurrence was detected on clinical and radiologic investigations, chemotherapy was discontinued at the end of the first year.

Nine months after the cessation of chemotherapy, the patient experienced numbness of the hands and colour changes after exposure to the cold. Physical examination showed tight, shiny and atrophic skin over the face and fingers (Fig. 1). There was also limitation of motion and atrophy of the finger muscles. These characteristic skin changes and the presence of Raynaud's phenomenon led us to examine the possible diagnosis of scleroderma. Because of the difficulty in swallowing, an oesophagogram was performed and dilatation of the oesophagus was revealed (Fig. 2). Peristalsis and passage through the oesophagus were found to be decreased. Cardiac and renal involvement were monitored by chest radiography, electrocardiography and 24-hour urine analysis (creatinine clearence and protein content) at diagnosis and at 6-month intervals thereafter. These tests were always normal. Pulmonary function tests revealed a mild restrictive defect. There was no evidence of bilateral pulmonary interstitial fibrosis on chest radiograph. Urinalysis, C_3, C_4, anti-nuclear antibody (ANA), anti-DNA and extractable nuclear antigen (ENA) were all within normal limits. However, the creatininin phosphokinase level was only slightly elevated in our patient. Electromyography did not show polymyositis. Rheumatoid factor was 20 IU/ml (normal: 0-20). Chest tomography was negative

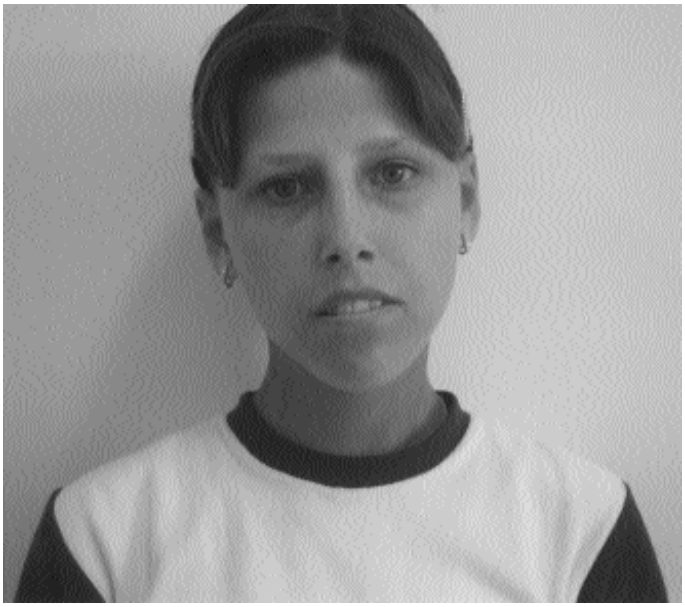

Fig. 1. Sclerodermatous appearance over the face.

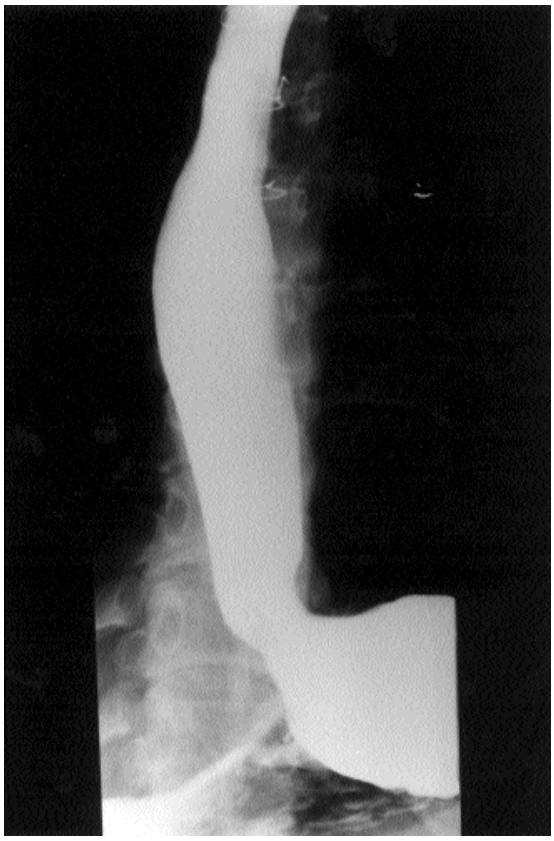

Fig. 2. Oesophagus showing marked dilatation.

for recurrence of the primary disease. Oral methotrexate was initiated at the dose of 10 mg/m^2/week. Because the attacks of Raynaud's phenomenon increased in severity, treatment was switched to D-penicillamine and prednisolone. Autoantibody tests repeated three months apart during the follow-up were all negative. Unfortunately we could not achieve any significant improvement in her symptoms during 14 months of follow-up.

Discussion

Scleroderma is one of the collagen disease with an increased risk of tumor development (4-6). Recently, Rosental *et al*. reported a 1.5 fold increase in all cancers among patients with scleroderma (5). Among them, lung and skin cancers showed the highest incidence. The frequency of cancer associated with scleroderma has been estimated to be between 3% and 7% in the adult population. The development of various autoimmune diseases after bone marrow transplantation (BMT) has been reported previously as well. These reports emphasize that any autoimmune disease, such as anti-phospholipid syndrome, autoimmune hepatitis, or bullous pemphigoid can occur following bone marrow transplantation (7). Chronic graft versus host disease, which is a frequent complication of BMT, also has clinical and pathologic characteristics similar to some autoimmune disease, particularly scleroderma and Sjögren's syndrome. It is reported that skin changes and the involvement of other organ systems in graft versus host disease after BMT were similar to those seen in patients with scleroderma (8).

Thus far, however, the association of scleroderma with cancer has not been reported in the pediatric age group. It is well known that scleroderma, particularly in its generalised form, is very uncommon in childhood. In one study, less than 10% of all scleroderma patients were under 16 years of age (9). This case presents the development of scleroderma in a pediatric case following chemotherapy for cancer. Although more than 8,000 children with malignant disease have been followed-up during the last 30 years in our hospital, we have not observed any other case of scleroderma among them. The coexistence of scleroderma and malignancy in our case suggests a possible connection between two conditions. Although an increased incidence of lung, skin and oesophageal carcinoma has been reported in patients with scleroderma, an association with thymic malignancy is very rare (10-12). Hsu *et al.* presented a case of thymic carcinoma associated with an autoimmune syndrome impressing scleroderma similar to our patient (13). Thymic carcinoma is one of the primary malignant lesions involving the thymus. A neoplasm of the thymus can be differentiated from other tumors involving the thymus, such as lymphomas, based on the presence of

the neoplastic epithelial components. Although various syndromes and diseases may be associated with thymomas including myasthenia gravis, polymyositis, systemic lupus erythematosus, and rheumatoid arthritis, the association with paraneoplastic syndrome is rarely reported in thymic carcinoma. Thymomas usually show an indolent clinical course, whereas thymic carcinomas are known to have a poor prognosis. Survival rates have been reported to be around 40-50%. Several mechanisms have been proposed for the association of malignancy and scleroderma in the literature. It is suggested that there is an increased incidence of malignancy in many diseases in which the tissue is subjected to persistant proliferation and repair. Comer *et al*. proposed that the cause of the development of scleroderma in their patient with lymphoma was a humoral or cell-mediated immune process initiated by malignancy (14).

Although scleroderma usually precedes the development of cancer and malignancy develops about 2-5 years after the diagnosis, scleroderma occurred when our patient was in remission after the discontinuation of chemotherapy (5). It is known that if an exacerbation or occurrence of scleroderma is observed in patients with malignancy, a recurrence of the underlying disease should be taken into consideration. But, there was no evidence to suggest tumor recurrence in our patient. The manifestations of scleroderma were present for a long time before the diagnosis of malignancy in most of the previous reports and usually appeared in organs affected by chronic fibrosing changes such as lungs, skin, oesophagus (10-13). It is proposed that chronic fibrosing degeneration may provide a predisposing factor for the development of malignancy. Such a mechanism was not possible in our case since scleroderma developed 20 months after the diagnosis of malignancy.

It is known that the administration of bleomycin may cause the development of scleroderma (15). There have also been some reports suggesting an association between Raynaud's phenomenon and the administration of certain chemotherapeutic agents such as bleomycin, vincristine, or cisplatin in the literature (16). We strongly suspect that the immunomodulating drugs used in our case may have played a role in the development of the patient's scleroderma.

In conclusion, we report the development of generalised scleroderma in a child who received combined chemotherapy for metastatic thymic carcinoma. This is the first reported case of scleroderma associated with malignancy in the pediatric age.

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