Cutaneous scleroderma in association with carcinoid syndrome

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Summary

A case of scleroderma in a woman with carcinoid syndrome is described and the similarities between our case and those in the literature are reviewed. The carcinoid tumours were all of midgut origin and liver metastases were present. All subsequently developed fibrotic heart disease and none had clinical features or auto-antibodies suggestive of systemic sclerosis. The association between carcinoid syndrome and particular features of scleroderma is likely to be more than fortuitous.

Keywords: scleroderma, carcinoid syndrome

Cutaneous scleroderma is part of a spectrum of diseases characterised by skin fibrosis and loss of elasticity. The pathogenesis is unclear. Carcinoid syndrome is a result of secretory products released by a carcinoid tumour, usually a gut primary with liver metastases. The secretory products of mid gut carcinoid tumours may be implicated in the pathogenesis of cutaneous scleroderma associated with carcinoid syndrome.

Case report

A 48-year-old woman presented in May 1983 complaining of intermittent diarrhoea and weight loss of 14 lbs over the preceding year. On direct questioning she admitted to episodes of facial flushing occurring over the previous 18 months. On examination she had facial telangiectasia, a cyanotic tinge over the cheeks and forehead, and four finger breath hepatomegaly. Investigations revealed a raised 24 hour 5-hydroxyindoleacetic acid level of 720 μmol (normal less than 50 μmol). Fine needle biopsy of a mass in the right lobe of the liver was consistent with a diagnosis of metastatic carcinoid.

Treatment was commenced with the oral serotonin antagonist, cyproheptadine, and subsequently with ketanserin and *p*-chlorophenylalanine. Her symptoms were not controlled and hepatic artery embolisation was undertaken on four occasions over the next two years. Each procedure resulted in symptomatic relief for approximately six months. The patient developed right heart failure due to tricuspid and pulmonary stenosis in September 1986 and responded well to balloon valvulo-

plasty. The original symptoms of carcinoid syndrome returned in November 1986 and treatment was started with the long-acting somatostatin analogue Octreotide (100 μg 8 hourly) which the patient administered by subcutaneous injection.

In November 1988 thickened and slightly tender patches of skin developed over both thighs (figure 1). Clinically this was thought to be localised scleroderma. Skin biopsy (figure 2) showing collagenisation of the reticular dermis extending below the sweat glands, with a mild chronic inflammatory infiltrate around the sweat glands and vessels at the dermal-fat junction, confirmed the diagnosis. There was no history of Raynaud's phenomenon or other features of systemic sclerosis. Auto-antibody profile including Scl 70 and anticentromere antibodies was negative. The skin changes progressed rapidly and in May 1989

Figure 1 Photograph of our patient's legs showing sclerodermatous patches on both thighs

Figure 2 Photomicrograph of a skin biopsy taken from our patient showing collagenisation of the reticular dermis which extends well below the sweat glands which are surrounded by a mild inflammatory infiltrate

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scleroderma affected both legs, abdominal wall, chest wall and upper arms. The patient's general condition deteriorated and alpha interferon was added to the treatment regime to try and regain sensitivity to somatostatin. Unfortunately there was no response to treatment and the patient died in August 1989, six years after the initial presentation.

Discussion

The pathogenesis of scleroderma is not entirely understood. Tryptophan and its metabolites have been implicated in the process. Therapeutic L-tryptophan has been associated with scleroderma-like lesions which improve with cessation of treatment.¹ Two stages in the pathogenesis of scleroderma have been described, early inflammatory and late sclerotic.² Serotonin when injected intradermally readily provokes inflammatory changes. Substance P and neurokinin A have both been shown to induce proliferation of human fibroblasts in vitro.³ Midgut carcinoid tumours produce substance P and neurokinin A whereas other carcinoid tumours do not.⁴

Serotonin reuptake inhibitors are useful in the treatment of carcinoid syndrome⁴ and may also be of use in scleroderma-related Raynaud's phenomenon.⁵ Interestingly, a beneficial effect of γ -interferon on systemic sclerosis has been suggested.⁶ The mechanism is thought to be due to inhibition of fibroblast proliferation and

Learning points

- localised scleroderma changes may occur in carcinoid syndrome
- there is overlap in the treatment of carcinoid syndrome and cutaneous scleroderma

collagen biosynthesis. α -Interferon may help regain sensitivity to somatostatin⁷ although this was not the case in our patient. There is considerable overlap in the treatment of carcinoid syndrome and cutaneous scleroderma. Substance P and neurokinin A antagonists such as Spandite³ may have a role in both the treatment and possibly prevention of carcinoid-associated scleroderma.

Scleroderma-like lesions in patients with carcinoid syndrome were first described by Zarafonitis *et al* in 1958⁸ and in total seven cases including ours have been reported.⁹⁻¹¹ These cases are similar: scleroderma first developed in the legs; the carcinoid tumours were all of mid gut origin and had liver metastases at the time of presentation; all subsequently developed fibrotic heart disease; none had clinical features or evidence of auto-antibodies associated with systemic sclerosis. The association of certain clinical features of carcinoid syndrome with cutaneous scleroderma seems to be more than fortuitous.

- 1 Connolly S, Quinby S, Griffin L. Scleroderma and L-tryptophan: a possible explanation of the eosinophilia-myalgia syndrome. *J Am Dermatol* 1990; 23: 451-7.
- 2 Lee EB, Anhalt GJ, Vorheef JJ, Diaz LA. Pathogenesis of scleroderma. *Int J Dermatol* 1984; 23: 85-7.
- 3 Nilsson J, Von Euler A. Stimulation of connective tissue cells growth by substance P and substance K. *Nature* 1985; 315: 61-3.
- 4 Saini A, Warman J. Management of carcinoid syndrome. *Postgrad Med J* 1991; 67: 506-8.
- 5 Black C. Scleroderma - clinical aspects. *J Intern Med* 1993; 234: 115-8.
- 6 Kahan A, Amor B, Menkef CJ, Strauch, G. Recombinant interferon gamma in the treatment of systemic sclerosis. *Am J Med* 1989; 87: 273.

- 7 Oberg K, Erikson B. The role of interferons in the management of carcinoid tumours. *Br J Haematol* 1991; 79 (suppl 1), 74-7.
- 8 Zarafonitis CJD, Lober S, Hanson S. Association of functioning carcinoid syndrome and scleroderma. *Am J Med Sci* 1958; 236: 1-14.
- 9 Asoboe-Hanson G. Scleroderma in carcinoid syndrome. *Acta Dermatol Venereol* 1959; 39: 270-3.
- 10 Hay DR. Malignant carcinoid syndrome with scleroderma. *NZ Med J* 1964; 63: 90-2.
- 11 Fries JF, Lindgren JA, Bull JM. Scleroderma-like lesions and the carcinoid syndrome. *Arch Intern Med* 1973; 131: 550-3.