

Case Report

Carcinoid Syndrome-Induced Scleroderma-Like Disease

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Keywords

Carcinoid syndrome · Scleroderma · Scleroderma-like disorders · Sclerodermoid disease · Skin

Abstract

Scleroderma is a rare complication of carcinoid syndrome and is usually encountered in the setting of a metastatic primary neuroendocrine tumour of the distal ileum. Associated endocardial fibrosis is a frequent finding and the condition carries a poor prognosis. We report a case of scleroderma occurring in a 72-year-old female with metastatic neuroendocrine carcinoma and associated pericardial fibrosis. The use of an alternative nomenclature such as “scleroderma-like” or “sclerodermoid” disease is proposed in order to emphasise its distinction from true idiopathic scleroderma, despite the histopathological similarities on skin biopsy.

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Introduction

Scleroderma is a rare complication of carcinoid syndrome, most often occurring in the setting of a metastatic neuroendocrine tumour of the distal ileum. Associated endocardial fibrosis is a frequent finding. Overall the condition carries a poor prognosis. We report a case of scleroderma occurring in a patient with metastatic neuroendocrine carcinoma with associated pericardial fibrosis.

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Fig. 1. Facial flushing of the cheeks, forehead and chin in carcinoid syndrome.

Fig. 2. Scleroderma-like erythema and tightness of the lower legs.

Case Report

A 72-year-old woman with a history of intestinal carcinoid syndrome presented in June 2018 for workup for severe erythema and tightness in her lower legs of 3 months' duration. She was known to have had a small intestinal carcinoid tumour (grade 1 neuroendocrine carcinoma), initially diagnosed in 2009. Surgical resection thereof had been undertaken. In January 2017 she had been diagnosed with carcinoid metastasis to the liver and lungs, as well as pericardial fibrosis.

On assessment the patient had a 3-month history of erythema over the lower legs accompanied by stiffness of the calves. She had a 1-month history of fixed facial flushing. She had been receiving monthly doses of 30 µg somatostatin/Sandostatin since April 2017. Her chromogranin A levels had steadily risen from 330.90 ng/L in January 2017 to 892.20 ng/L in June 2018. On examination there was visible flushing of the cheeks, chin and forehead accompanied by cyanosis and telangiectasia (Fig. 1). The lower legs were extremely erythematous and taut (Fig. 2). There was a reduced range of motion in the knees and ankles. She had no Raynaud's phenomenon.

Results

Autoantibody screening including Scl-70 and anticentromere antibodies was negative. Echocardiography and computerised tomography scanning revealed mild pericardial fibrosis but no endocardial changes. A skin biopsy from the leg showed a somewhat expanded dermis, with increased collagenisation and a diminished number of cutaneous adnexal structures (Fig. 3). Some of the eccrine sweat gland coils in particular appeared "bound down" by the altered collagen and showed a concomitant loss of their normal surrounding contingent of adipocytes (Fig. 4). There was a relatively abrupt demarcation between the deep dermis and the underlying superficial subcutaneous fatty tissue, with thickening of individual dermal

Fig. 3. Medium-power photomicrograph of the skin biopsy showing dermal thickening as a result of sclerodermoid alterations, as well as a paucity of adnexal structures. There is artefactual clefting as a consequence of the changes in the dermal collagen.

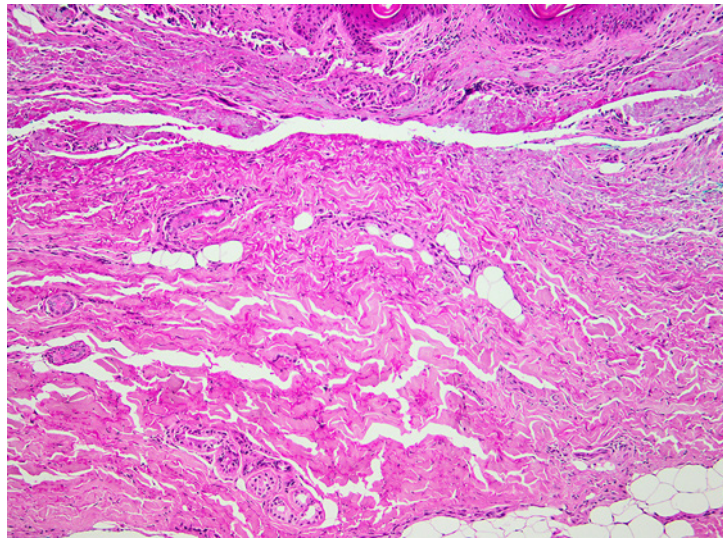
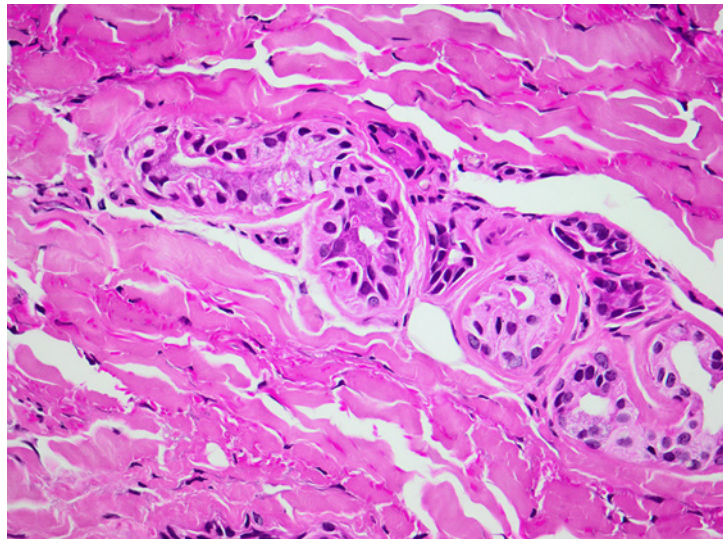


Fig. 4. Eccrine sweat gland coil “bound down” by the abnormal surrounding collagen, with a commensurate loss of the normal surrounding contingent of adipocytes.



collagen bundles and a subtle increase in the number of fibroblasts (Fig. 5). The described changes in the dermal collagen were accentuated on staining with the Masson trichrome method (Fig. 6). There was no evidence of calcinosis cutis, and histochemical stains for amyloid, mucin and elastin did not reveal any abnormalities. The aforementioned findings, in the setting of metastatic carcinoid syndrome, were consistent with carcinoid syndrome-induced scleroderma-like disease. The patient’s condition continued to deteriorate, and she died in July 2018, 4 months after the onset of her cutaneous symptoms.

Discussion

Carcinoid tumours are rare neuroendocrine tumours, usually of the small intestine, and arise from enterochromaffin cells. The overall incidence is about 1.5 per 100,000. Malignant carcinoid syndrome refers to a complex of tumour-related clinical features and is encountered in less than 10% of patients with carcinoid tumours [1]. Carcinoid syndrome symptoms

Fig. 5. Sharp demarcation of the interface between the deep dermis and the subcutaneous compartment. The dermal collagen bundles appear somewhat swollen and sclerotic.

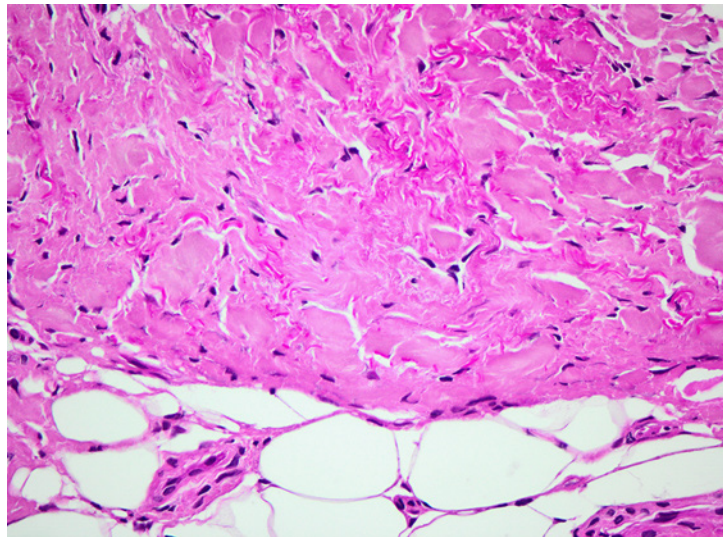
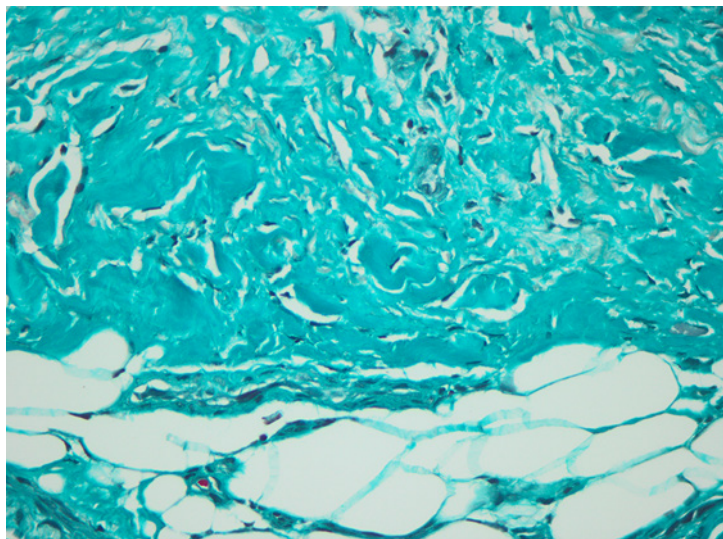


Fig. 6. Masson's trichrome stain highlighting the changes in deep dermal collagen depicted in Figure 5.



include diarrhoea, abdominal cramps, dyspnoea, asthma and cutaneous symptoms such as flushing, pellagra and scleroderma-like changes [2].

Carcinoid tumours are thought to cause carcinoid syndrome through the release of neuroendocrine chemicals such as serotonin, substance P, histamine, dopamine, neurotensin and tachykinins [3]. Carcinoid syndrome usually occurs in the setting of metastatic disease to the liver, whereby chemicals are able to bypass liver metabolism [4]. Flushing is the commonest symptom and has been classified into several different subtypes. Flushing can be limited to the face or can extend to the neck and trunk [5]. Flushing tends to occur as repeated attacks ultimately resulting in persistent erythema and a rosacea-like appearance of the face and neck [6]. Foregut tumours have been reported to cause more of a pink/red flush related to the release of histamine, whilst midgut tumours are more likely to produce a cyanotic flush related to the release of the vasodilating peptide bradykinin, histamine, serotonin and prostaglandins [1].

Pellagra dermatitis is a condition of niacin (vitamin B3) deficiency. It presents as a photo-distributed, scaly rash associated with glossitis and angular stomatitis. Systemic symptoms

include diarrhoea and encephalopathy. Dietary tryptophan is the precursor of both serotonin and niacin. In carcinoid syndrome, increased serotonin production outpaces dietary intake of tryptophan. This results in a niacin deficiency. Adequate supplementation with nicotinamide is the recommended management [6].

Scleroderma secondary to carcinoid syndrome is rare and was first described by Zaranfonetis et al. [7] in 1958. The exact mechanism of fibrosis is unknown, but there are several proposed theories. In general, scleroderma-like disease is considered a feature of carcinoid tumour arising from the distal ileum [8]. While serotonin and tryptophan have been shown in vitro to induce fibrosis, Handley et al. [8] proposed that substance P and neurokinin A were more likely culprits [8, 9]. Substance P and neurokinin A are exclusively produced by terminal ileal tumours and are therefore more likely mediators [8].

Scleroderma associated with carcinoid syndrome tends to involve the lower limbs before the upper limbs and generally spares the hands and feet. Autoantibodies are negative, there is an absence of Raynaud's phenomenon, and there is a lack of non-cardiac visceral involvement [2]. Associated endocardial fibrosis, however, is a common feature [1]. The latter is a poor prognostic marker and is most often irreversible [2].

Treatment of scleroderma in this setting of carcinoid syndrome is a challenge. There have been isolated reports of improvement with octreotide [10]. The condition carries a poor prognosis. The diagnosis should prompt assessment for associated endocardial fibrosis [2, 4]. Although the term "scleroderma" is commonly applied in this clinical context, we propose the use of an alternative nomenclature such as "scleroderma-like" or "sclerodermoid" disease in order to emphasise the condition's distinction from true idiopathic scleroderma – despite the obvious histopathological similarities on skin biopsy.

Acknowledgements

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Statement of Ethics

Signed patient consent was received and ethics committee clearance was obtained from the relevant authorities.

Disclosure Statement

The authors have no conflicts of interest to declare. No funding was required for this case report.

Author Contributions

K.K. was responsible for interviewing the patient and providing clinical support. Both authors collaborated in the literature search, as well as in the drafting, correction and submission of the manuscript. The clinical images were provided by K.K. W.G. was responsible for the photomicrography. Both authors read and approved the final manuscript.

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