

Systemic sclerosis induced by interferon-alfa treatment of melanoma

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ABSTRACT

Systemic sclerosis is a connective tissue disease characterized by a complex pathogenesis and a multi organ involvement of unknown etiology. Genetic features and environmental factors, as the use of some drugs, influence the onset of the clinical picture. The authors describe a case of a patient who developed systemic sclerosis after treatment of melanoma with interferon alfa-2b, a drug rarely implicated in the induction of this disease.

Keywords: Systemic sclerosis; Scleroderma; Interferon alfa-2b.

INTRODUCTION

Systemic sclerosis (SSc) is a complex and heterogeneous disease, characterized by a massive deposition of collagen and other matrix substances in skin and multiple internal organs, alterations of the microvasculature, as well as disturbances of the immune system¹. Its etiology is subject to ongoing research, since the exact nature of the events underlying this disease remains unclear. Genetic and environmental factors have been linked to SSc and, among these some drugs appear to influence the onset of clinical symptoms, such as bleomycin, L-tryptophan and taxane²⁻⁴. Interferons (IFNs) are well-known immunomodulators and inhibitors of collagen production. However, some studies also showed an increase mRNA and protein levels of IFNs and several interferon stimulated genes in cells and tissues from SSc patients⁵.

There are just few cases reported in the literature suggesting an association between IFN and the occurrence of SSc⁶⁻⁹.

CASE REPORT

A 56 year old female patient had been diagnosed melanoma, located on the right thigh, with lymph nodes metastasis (ipsilateral inguinal region), at the age of 45. She was submitted to lymph node dissection and adjuvant therapy with interferon alpha 2b. Simultaneously, she described the appearance of episodes consistent with Raynaud's phenomenon in the hands and feet and skin thickening on the hands and face. Ten years later, symptoms suggestive of gastroesophageal reflux started. No pulmonary or cardiac symptoms were reported. In 2013 she was admitted in our Rheumatology department with the onset of new digital ulcers. On physical examination, we confirmed the Raynaud's phenomenon and the presence of thickened skin (face, hands), sclerodactyly and telangiectasies (labial, face and chest) as shown in Figure 1. Her oral aperture was reduced to 3.5 cm. The blood tests showed positive antinuclear antibodies (ANA), with a speckled pattern, a titer of 1/640 and anti-centromere positive. Capillaroscopy revealed typical scleroderma pattern with



FIGURE 1. Systemic sclerosis manifestations of our patient

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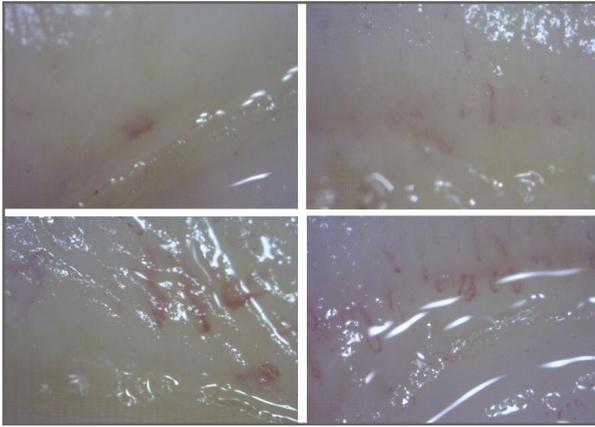


FIGURE 2. Late SSc pattern shown in capillaroscopy

low density of capillaries, disorganization of the normal capillary array and few giant capillaries (Figure 2). The computerized axial tomography of chest excluded pulmonary involvement but indicated esophageal dilatation in all its extension. The diagnosis of limited cutaneous *systemic sclerosis* with esophageal involvement was made.

DISCUSSION

SSc has an increased association with certain malignancies and it can present as a paraneoplastic syndrome. Although this patient had a recent diagnosis of melanoma, the absence rapidly progressive skin sclerosis extending to the neck and trunk and the positive antibodies decreases the likelihood of the paraneoplastic syndrome. This patient was treated with interferon alfa-2b, a drug rarely implicated in induction of scleroderma. However, it is known that IFN has multiple effects on the immune system.

Coelho *et al.* discussed about an etiopathogenic role for IFN system in scleroderma, and, according to these authors, the IFN α/β produced promotes dendritic cells development, T cell activation and autoantibody production by B cells. DNA or RNA and associated proteins form immune complexes that could act as endogenous IFN inducers that cause prolonged production of IFN. This further stimulates the autoimmune response as a consequence of more autoantibody production and immune complexes formation. The produced IFNs could also induce an apoptotic and antiangiogenic state on endothelial cells contributing to vascular damage in SSc¹⁰.

A placebo-controlled randomized study has examined IFN alfa as a possible treatment for SSc. In this trial, IFN worsened some SSc manifestations supporting the possibility that this treatment can contribute to skin sclerosis¹¹.

In conclusion, the concomitant onset of therapy with interferon alfa-2b and the clinical symptoms with typical cutaneous involvement, positive ANA and the fact that patient had already spent ten years without cancer relapse, supported systemic sclerosis induced by interferon-alfa diagnosis.

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