

## Paraneoplastic Scleroderma: Are There Any Clues?

Dear Editor,

Scleroderma associated with neoplasia is rare, with only a small number of cases reported. We describe 4 patients with paraneoplastic scleroderma who were treated at the I. Department of Dermatovenereology, St. Anna Hospital, during the period between 2004 and 2014. The patients were diagnosed with cholangiogenic carcinoma, endometrial carcinoma, prostatic adenocarcinoma, and adenoma of the suprarenal gland.

In the case of concurrent scleroderma and tumor, four situations may occur: they can develop independently of each other; scleroderma may be induced by the tumor; the tumor can develop in the scleroderma; or the tumor can be induced by immunosuppressive therapy.

Sclerotization of the skin was described in association with lung cancer, carcinoid, plasma cell dyscrasia, cancer of the ovary, cervix, breast, esophagus, stomach, nasopharynx, melanoma, and sarcoma (1,2,5,7,10).

Symptoms may be induced by substances secreted by the tumor (hormones, cytokines, etc.) (9). Tumorous cells further induce cytotoxic and autoantibody response.

Scleroderma is characterized by immunological dysregulation, vasculopathy, and hyperproduction of the extracellular matrix by activated fibroblasts. Endothelial, inflammatory, and mesenchymal cells produce cytokines, chemokines, and growth factors e.g. Interleukin-1 (IL1), Interleukin-6 (IL6), tumor necrosis factor alpha (TNF  $\alpha$ ), collagen alpha 1, connective tissue growth factor (CTGF) (3), and basic fibroblast growth factor (bFGF). This factor is also produced by lung cancer cells (4).

The clinical picture of scleroderma and paraneoplastic scleroderma is similar. Diffuse thickening of the skin and/or sclerodermatous plaques can be seen. The histological picture is consistent with scleroderma.

Capillaroscopy changes, antinuclear antibodies (ANA), sclerodactyly, and Raynaud phenomenon suggest the diagnosis of systemic scleroderma (SS) (4).

Our patients did not fulfill enough of the criteria for SS. Both diffuse and localized scleroderma was seen in 3 patients and generalized localized scleroderma in one case. All patients had a histological picture consistent with scleroderma, negative ANA and ENA antibodies (Table 1, Figure 1).

A 66-year-old woman presented with a 10 months history of sclerodermatous plaques on her neck, trunk, and upper and lower extremities. The skin on her breasts and cheeks was diffusely indurated. Examination showed thrombocytopenia, elevated transaminases, Cancer antigen 19-9 (Ca 19-9), thyroid stimulating hormone (TSH), and anti-thyroid peroxidase antibodies, dysmotility of the lower part of esophagus, hepatosplenomegaly, cholecystolithiasis,



**Figure 1.** a) diffuse induration on the forearms; b) diffuse induration and scleroderma patches on the legs; c) scleroderma patch in the lumbar area, d) diffuse induration on the thighs.

**Table 1.**

Patient No	Age at diagnosis of neoplasia	Sex	Time to diagnosis of neoplasia/duration of scleroderma	Extent	Systemic scleroderma signs	Cancer/neoplasia
1	66 years	F	10 months	Cheeks, neck, breasts, abdomen, back, upper extremities, lower legs	Oesophagus dysmotility	Cholangiogenic cancer
2	74 years	F	36 months	Upper and lower extremities, trunk, genital area	Vasoneurosis - toes	Endometrial cancer
3	80 years	M	1 month	Lower legs, thighs, forearms, trunk	Capilaroscopy changes - toes	Prostate cancer
4	62 years	F	2 months	Upper and lower extremities, back, abdomen, breasts	Lung hypertension	Suprarenal adenoma
Mean age/ duration	70,5 years		12 months			

and benign polyps of colon. She was given prednisone 40 mg/day but did not return for follow up. After 6 months she was diagnosed with cholangiogenic carcinoma with metastatic disease and died shortly afterwards.

A 74-year-old woman had localized scleroderma on the trunk for three years. She was treated with procaine penicillin for positive borrelia Immunoglobulin M (IgM) antibodies. Her condition worsened suddenly with confluent scleroderma plaques on her trunk, extremities, and genital region, and vasoneurosis on her lower extremities; she was started on prednisone 35 mg/day. Examination revealed endometrial cancer. The patient underwent a hysterectomy, adnexectomy, and radiotherapy with curative effect. Scleroderma patches softened with residual hyperpigmentation, and prednisone was stopped two years later.

A 80-year-old man had a month-long history of diffuse thickening and toughening of the skin on the forearms and lower legs and scleroderma patches on the thighs and shins. Examination revealed prostate adenocarcinoma, and therapy with antiandrogen bicalutamide and prednisone 15 mg/day was started. Two years after the diagnosis he continues with bicalutamide treatment, prednisone 5 mg q.a.d. and has residual toughening of the skin on his lower legs.

A 62-year-old woman with seronegative rheumatoid arthritis presented with diffusely tough skin on her extremities and trunk, present for 2 months. Examination revealed cervicitis with a benign endometrial polyp, cholecystolithiasis, borderline pulmonary hypertension, and a hormonally inactive suprarenal

adenoma. She was given prednisone 40 mg/day and penicillamine with effect. In the 3rd year of therapy she has residual induration of her lower legs and a scleroderma plaque in the lumbar region. She is monitored for her suprarenal adenoma.

Two patients had scleroderma at the same time as a malignant tumor; in one patient the localized scleroderma worsened rapidly at the time of the tumor diagnosis, and in one patient a clinically silent adenoma was found. Adrenal tissue can secrete molecules such as serotonin or bFGF involved in fibroplasia (3,6). One patient died of a metastatic disease, two patients after the successful treatment of the tumor, and the patient with suprarenal adenoma experienced softening of the skin and regression of scleroderma.

Although paraneoplastic scleroderma is often classified as a pseudoscleroderma, we regard neoplasia as a distinct triggering impulse for scleroderma. Recently, an association between RNA polymerase I/III antibodies in systemic scleroderma and cancer was suggested (8). Such studies may confirm the true link between scleroderma and malignancy. These patients are characterized by older age, sudden onset, diffuse thickening of the skin, and/or generalized morphea with a concurrent neoplastic process. In the case of a successful tumor treatment, skin changes regress.

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