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Case Report

A Role for Nailfold Video-Capillaroscopy in Paraneoplastic Systemic Sclerosis

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Abstract

Systemic sclerosis is a rare autoimmune disease characterized by small vessel vasculopathy and fibrosis. It is associated with an increased risk of cancer compared to the general population, and it can also be regarded as a paraneoplastic manifestation. As such, signs and symptoms of systemic sclerosis should regress after treatment of the underlying neoplasm. One of the earliest signs of systemic sclerosis is Raynaud's phenomenon, with characteristic nailfold video-capillaroscopy abnormalities. We describe the case of a patient who was diagnosed with breast cancer after systemic sclerosis onset. After treatment for breast carcinoma, her systemic sclerosis did not progress, and the abnormalities found on nailfold video-capillaroscopy showed considerable regression, suggesting the paraneoplastic nature of SSc.

Keywords: Systemic sclerosis; Raynaud's phenomenon; Nailfold video-capillarsocopy; Cancer

Introduction

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease characterized by small vessel vasculopathy leading to fibrosis of involved organs, especially the skin but also the lungs, kidneys, and gastrointestinal tract [1]. One of the earliest signs of SSc is Raynaud's phenomenon (RP), defined as the sequential colour change of one or more fingers that become pale white (ischemic phase), then blue (cyanotic phase), and eventually red (post-ischaemic hyperaemia); sometimes RP is associated with acral pain and numbness. RP is typically triggered by exposure to cold or emotional stress, which causes excessive vasospasm of digital capillaries [2]. It can be benign in otherwise healthy individuals (primary RP), while we refer to secondary RP when it precedes or concurs with other manifestations of systemic autoimmune diseases, such as SSc (especially when accompanied by digital ulcerations) [3]. The instrumental examination of choice to discriminate between primary and secondary RP is nailfold video-capillaroscopy (NVC), a non-invasive procedure that magnifies, through a handheld microscope, capillaries located in the dermis of the epinichyum. This technique allows the recognition of three main patterns of vascular abnormalities, called "early", "active," and "late" scleroderma patterns, according to the stage of the disease in which they are more frequently found. Few capillary haemorrhages and giant capillaries characterize the early scleroderma pattern; the active pattern comprises frequent giant capillaries (or mega-capillaries) and haemorrhages, with architectural disorganization and moderate loss of capillaries, whereas in the late pattern, structural changes in the capillary network predominate and avascular areas and neoangiogenesis are found [4].

It is well known that SSc is associated with a relatively higher cancer incidence compared to the general population, especially for lung, liver, bladder, and hematologic cancers, though the absolute risk is relatively low. The incidence of cancer appears to be higher during the first year after a diagnosis of SSc is made [5]. However, it is not clear if a causal relationship really exists. Many hypotheses have been formulated, including the possibility that cancer induces the development of scleroderma and vice versa [6]. SSc can therefore represent a paraneoplastic syndrome; accordingly, symptoms should regress after successful treatment or surgical removal of the underlying neoplasm. Since SSc can have an indolent course itself, it is not always easy to ascribe the steadiness or improvement of SSc to a successful cancer treatment.

This report describes the case of a patient who had breast cancer diagnosed after 19 months from SSc onset, accompanied by improvement of NVC abnormalities after successful treatment of the neoplasm.

Case Presentation

A 50-year-old non-smoker woman presented to our hospital for the first time in November 2012 with a history of RP without ulcers since adolescence, photosensitivity, frequent oral aphthae, and dyspnea for mild efforts. A rheumatologist recorded acrocyanosis, puffy hands, and mild oedema of both legs at the first visit. The modified Rodnan skin score (mRSS) was five (predominant involvement of fingers and hands). Laboratory tests were ordered, which revealed positive anti-nuclear antibodies (ANA) at titre >1:640 with nucleolar and speckled patterns at the indirect immunofluorescence (IIF) assay, negative extractable nuclear antigen (ENA) screening (solid phase assay), and mild C4 consumption. A NVC showed a "*very*" early scleroderma pattern (because of the presence of pre-giant capillaries, micro-haemorrhages, and altered capillary architecture), with the evolution of some pre-giant capillaries into complete giant capillaries

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one year later **(**Figures 1A, 1B**)**. A diagnosis of early limited cutaneous (lc) SSc was made in accordance with LeRoy and Medsger's 2001 classification criteria [7], and additional tests were performed. A high-resolution computed tomography (HRCT) of the chest revealed initial aspects of interstitial lung disease, with initial bilateral thickening of interlobular septa and mild bibasal, dorsal ground glass opacities (GGO), Goh's score 10 **(**Figure 2A**)**. No pharmacological treatment was deemed necessary, and the patient underwent only tight follow-up. Pulmonary function tests (PFTs) demonstrated no reductions in air flows but a reduced carbon monoxide diffusion lung capacity (DLCO, 57% of predicted, partially corrected by alveolar ventilation), which provedstable or minimally improving at follow-up without any specific treatment. Oesophageal scintigraphy with Technetium 99m Sulphur colloidrevealed grade two oesophageal dyskinesia with increased transit time of solid meals. Laboratory tests also revealed a previous contact with hepatitis B virus (HBV) without detectable HBV-DNA.

Eight months later (July 2013), a mammogram and a breast ultrasound (performed for a stinging feeling in the right breast) revealed the presence of micro cysts, but no further treatment was deemed necessary. On July 14, 2014, the patient underwent a right quadrantectomy with excision of a sentinel lymph node; she was diagnosed with an invasive lobular breast carcinoma staged pT2N0sM0. Pathological analyses revealed oestrogen receptor expression at 80%, progesterone receptor at 80%, Ki67 at 15%, and human epidermal growth factor receptor (HER)-2 positivity. She also received adjuvant chemotherapy (four cycles of epirubicin and cyclophosphamide) first, then radiotherapy (50 Gy/25 F) from January to February 2015, and hormone therapy (daily oral tamoxifen and leuprolide; the former was substituted by letrozole in 2017 due to the occurrence of endometrial thickening). She was followed up by oncologists at another centre; no relapse was observed. Therefore, hormone therapy was interrupted in December 2021, and only yearly clinical follow-up was advised.

At contemporary rheumatologic follow-up, SSc did not demonstrate signs of evolution; she underwent cardiac Doppler ultrasound, which found no pulmonary arterial hypertension (estimated pulmonary arterial systolic pressure of 23 mmHg). Arthralgia due to osteoarthritis was treated with analgesics (paracetamol or mild opiates) with some benefit.

In March 2022, 30 months after her last in-person visit (retard also due to the COVID pandemic), she presented in our ambulatory clinic complaining of mild dysphagia, arthro-myalgias, and stable dyspnoea for moderate efforts. She had also noted the appearance two years before of fissured self-limiting lesions on the palmar face of the fingers and hands, especially during cold months; she also admitted long-term permanence outdoors without adequate protection. She had performed PFTs in 2018 and again in 2022, showing a significant worsening of DLCO through the years, from 102.7% to 63% of what was predicted.

A restaging of her disease was deemed necessary. At clinical evaluation, regression of dermal sclerosis was detected with an mRSS of one; no ulcers were evident, but scratches were visible on the fingers of both hands. Questioned about her RP, the patient referred to the fact that she had not noticed significant digital colour changes since about the beginning of cancer treatment, although sometimes her fingers and palms get reddish (without clear association with cold exposure).

PFTs were repeated, confirming a mild to moderate reduction of single-breath DLCO (54% of predicted), partially corrected by alveolar ventilation (77%), similar to the results obtained at disease onset. The autoimmune profile was reassessed: ANA proved positive (same titre and patterns), ENA screening (FEIA method) was negative, with only a borderline positivity for PL-7. A new chest HRCT was performed, which showed only mild progression of subpleural reticulations in bilateral dorsal lower lobes with quite stable GGOs, compatible with a probable usual interstitial pneumonia (UIP) pattern **(**Figure 2B**)**.An otorinolaryngoiatrist evaluated the patient for dysphagic symptoms using fibrolaringoscopy but found neither an anatomical nor functional deficit, thus attributing dysphagia to the absence of some teeth. Cardiac Doppler ultrasound revealed a slightly increased PAP, now estimated to be 30 mmHg, possibly due to concomitant tricuspid valve insufficiency. A multidisciplinary evaluation, including specialists in rheumatology, pulmonology, and radiology, was performed; by comparison between previous and actual HRCT scans, only a small progression of pulmonary lesions was recognized. Considering the substantial stability of lung involvement after a long time interval (nine years), a watch and wait strategy, repeating the HRCT at 12-month intervals, was adopted. No background-specific therapy was prescribed.

A new NVC was performed. Surprisingly, all the previous observed capillary anomalies had vanished **(**Figure 3**)**; nailfold capillaries had a normal loop course and normal diameter, with only a few cross-capillaries, judged not specific for a scleroderma pattern anymore.

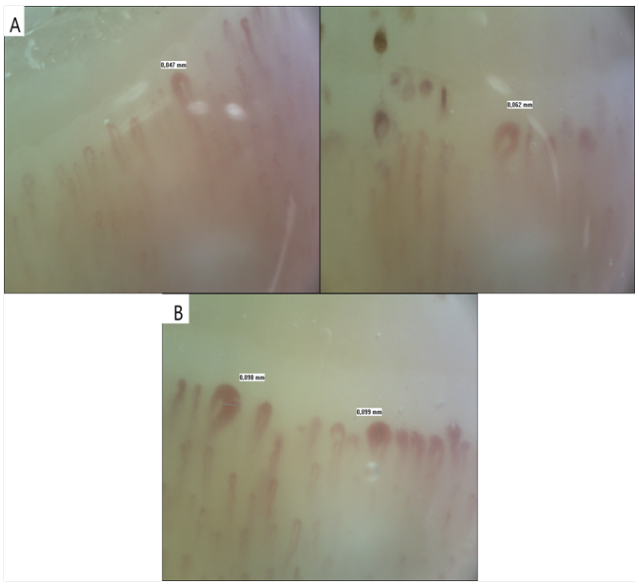

Figure 1: (A) Nailfold videocapillaroscopy (NVC) of third and fourth right finger, performed in 2012 and shows enlarged loops, a mega capillary and micro bleedings. **(B)** Fourth right finger in 2013 and increased number of mega capillaries.

Discussion

To the best of our knowledge, there are few reports in the literature describing improvement of SSc signs and symptoms after treatment of concomitant neoplasms. Moreover, only in a minority of these cases was NVC performed before and after cancer treatment, with variable results (normalization in one case and confirmation of the previous normal or slightly altered pattern in two others) [8, 9].

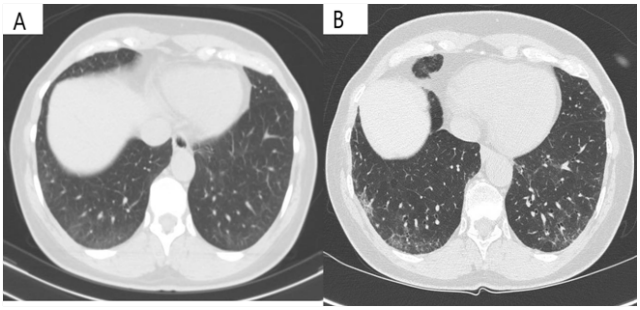

Figure 2: High-Resolution Computed Tomography (HRCT) of the Chest. **(A)** Scan performed in 2013, showing initial bilateral thickening of interlobular septa and mild bibasal, dorsal ground glass opacities (GGOs). **(B)** The same scan, 9 years later: stable bibasal GGOs, mild progression of subpleural reticulations in bilateral, dorsal lower lobes.

Figure 3: Nailfold videocapillaroscopy (NVC) of fourth right finger performed in 2022. Note the quite regular shape and dimensions of capillary loops, with only few enlarged loops, compared to 2013 NVC see in figure 1.

Improvement in disease management through recent years has led to a reduction in SSc-associated mortality, paralleled by an increase in mortality for causes other than SSc itself, with cancer being one of these leading causes [10].

As for other autoimmune diseases (such as idiopathic inflammatory myositis and vitiligo), it has been postulated that cancer is a source of abnormal tissue antigens (eliciting the production of autoantibodies that cross-react with normal tissue antigens elsewhere in the body) in SSc patients as well. This is further supported by the finding that in anti-RNA polymerase III-positive patients who develop a neoplasm, both cancer diagnosis and SSc onset occur within two years of one another [11]. Therefore, SSc can also be seen as a paraneoplastic manifestation of a pre-existing tumour; eliminating the source of the above-mentioned antigens should prompt the cessation of the autoimmune response. Moreover, SSc symptoms may develop as a consequence of treatment with immune checkpoint inhibitors, which stimulate adaptive immunity [12].

On the other hand, SSc-related fibrosis of one organ can be a risk factor for the development of a neoplasia in that organ; this is especially true for lung cancers [13]. Nonetheless, SSc treatments, such as cyclophosphamide used for interstitial lung involvement, are cytotoxic and favor the onset of neoplasia. Finally, it has been suggested that SSc and cancer may share environmental exposures (e.g., silica dust), genetic background, and pathogenic mechanisms (such as epithelial-to-mesenchymal transition) [14].

We are aware that the interval of 19 months between the diagnosis of SSc and the discovery of breast cancer represents a long time interval and that SSc showed a mild severity and a slow rate of progression.

However, the time framework is compatible with a cancer-incited SSc [11]. Moreover, soon after the diagnosis of SSc, she was treated for breast cancer, with no relapses until now and an overall stabilization of the underling autoimmune disease since then. Lung imaging remained quite stable, while cutaneous involvement showed only a little, although detectable, improvement by mRSS.

Interestingly, NVC showed the clearest improvement. Since microangiopathy is considered an early sign of SSc and an essential step in the physiopathology of the disease, one can speculate that the removal of the neoplasm could have had a favorable effect on microvascular changes (and, therefore, on the appearance of capillaries at NVC).

Finally, PL-7 positivity and interstitial lung involvement, together with arthralgias and the "*mechanic's hands*" appearance of the fingers, could raise the suspicion of an anti-synthetase syndrome; however, clinical and laboratory signs suggestive of a myositis were absent.

Changes in NVC are already employed as an outcome measure in at least two ongoing trials exploring the effects of therapies directed against SSc pathophysiological pathways (i.e., hematopoietic stem cell transplantation vs. cyclophosphamide and intramuscular administration of allogeneic mesenchymal stromal cells, respectively) on the SSc course [15, 16].

Our case highlights the potential role for NVC as a quick and non-invasive exam to assess and follow up on the evolution of a possibly cancer-related SSc after treatment of the primitive neoplasia.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

The patient in this manuscript has given written informed consent to publication of the case details.

Availability of data and materials

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

Conflict of interests

None.

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Author's contribution

G.G. wrote the manuscript, with the support of A.M., F.R. and M.P.; M.G. supervised the manuscript. All authors read and approved the final manuscript.All authors discussed the results and contributed to the final manuscript.

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