ISSN 2786-6661
eISSN 2786-667X

UDC: 618.19-006-085.849-06:616-092.19-004]-074-08
https://doi.org/10.32345/USMYJ.2(154).2025.115-121

Received: April 15, 2025
Accepted: June 11, 2025

Radiation-induced systemic sclerosis in a breast cancer patient: a case report

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Abstract: *Systemic sclerosis is a rare chronic autoimmune disease characterized by progressive fibrosis, vascular dysfunction, and immune system activation, leading to significant morbidity. While localized skin fibrosis, known as morphea, is a recognized complication of radiation therapy, the development of systemic sclerosis following radiation exposure remains extremely rare. . A consistent finding across all reported cases is the anatomical site of the malignancy -the breast- suggesting a unique vulnerability of this tissue and a potential site-specific predisposition to post-radiotherapy sclerotic changes. This case highlights the onset of systemic sclerosis in a breast cancer survivor after receiving adjuvant radiotherapy, emphasizing the complexities of early recognition and management. A fifty-year-old female with no prior history of autoimmune disease presented with progressive skin tightening, Raynaud's phenomenon, joint stiffness, and difficulty swallowing several months after completing radiation therapy for breast cancer. Diagnostic workup revealed positive anticentromere B antibodies, soft tissue calcinosis, and esophageal dysmotility, confirming the diagnosis of limited systemic sclerosis according to ACR/EULAR, 2013 criteria. The patient was initiated on immunosuppressive therapy, vasodilators, and supportive care for gastrointestinal dysfunction, leading to partial symptomatic improvement. The pathophysiology of radiation-induced systemic sclerosis is not yet fully understood, but it is believed to involve microvascular endothelial damage, immune dysregulation, and fibroblast activation. Existing evidence suggests that radiation therapy may act as a triggering factor in genetically predisposed individuals, leading to the unmasking of latent autoimmune processes. Delayed diagnosis can result in irreversible fibrosis, multi-organ involvement, and significant functional impairment, underscoring the importance of vigilance in high-risk patients. A multidisciplinary approach involving rheumatologists, oncologists, and supportive care personnel is essential to optimize outcomes. Early intervention with immunomodulatory therapies and targeted symptom management can help mitigate disease progression and improve quality of life. Further research is needed to clarify the mechanisms underlying radiation-induced systemic sclerosis, assess potential risk factors, and develop preventive strategies. Identifying immune alterations associated with post-radiation fibrosis may facilitate personalized approaches to screening and early intervention in individuals undergoing radiation therapy. Increasing awareness of this rare but serious complication can lead to earlier diagnosis, timely treatment, and improved prognosis in affected patients.*

Keywords: Breast cancer, Radiotherapy, Systemic sclerosis.

ISSN 2786-6661
eISSN 2786-667X

Introduction

Systemic sclerosis (SSc) is a complex autoimmune disorder characterized by immune activation, vasculopathy, and excessive collagen deposition, resulting in multi-organ fibrosis. The pathogenesis of SSc remains elusive but is thought to involve genetic susceptibility, environmental triggers, and aberrant immune responses [1, 2]. Radiation therapy (RT) is a cornerstone treatment for breast cancer, yet it carries potential long-term complications, including fibrosis and radiation-induced secondary malignancies [3]. While localized SSc following RT is well documented, cases of diffuse SSc post-radiation are exceedingly rare and are reported only in some isolated case reports [4, 5, 6]. Given the increasing survivorship of breast cancer patients, recognizing rare autoimmune complications like radiation-induced SSc is imperative for early intervention and improved prognostic outcomes [4].

Recent literature has suggested that radiation may trigger autoimmune responses, potentially through mechanisms such as endothelial damage and immune dysregulation. A recent case study reported by Nimbark D. et al. [5] described a similar case of radiation-induced SSc, highlighting the diagnostic challenges and potential therapeutic interventions. Additionally, emerging evidence from Du A.X. et al. [4] discusses the role of radiation in immune-mediated connective tissue disorders, reinforcing the need for further research on this association.

Case Report

The patient is a 50-year-old female who was diagnosed with left-sided non-metastatic breast cancer (T2N0M0) in 2022. She underwent a mastectomy in July of 2022, and it was followed by adjuvant radiotherapy. By September 2022, RT was complete and she had received a total dose of 40 Gy. The patient had no previous autoimmune disorders or connective tissue diseases and did not take any chemotherapeutic treatment for her cancer.

In May 2023, the patient visited the hospital with complaints of swallowing difficulties, heartburn and mild joint pain. Over the course of a few months her symptoms worsened, and there was marked hyperpigmentation over the area of her chest where RT was received. She had general weakness, headache, and complained of shortness of breath when climbing to the 3rd floor. The patient had a dry cough with mucous membrane discharges. Further, by the next year, compaction of the skin of the hands was noticed and the patient expressed a concern of episodic whitening and blueness of fingers and toes in response to cold.

The patient's general condition was satisfactory, and normosthenic. The respiratory exam was normal showed vesicular sounds, no wheezing, and the chest CT scan showed no evidence of interstitial lung disease. Cardiac condition was good too with slightly muted tones but no border shifts or any other deviations from the norm.

On clinical examination, her skin showed induration. The modified Rodnan Skin Score (mRSS) was 12. There was hyperpigmentation, the patient had a shiny mask-like face with a purse-string mouth (Fig. 1). She had a pitting scar after ulceration of the 3rd finger of the right hand and cutaneous calcinosis was seen on the ulnar part of the left forearm and her right buttock (Fig. 2 and 3 respectively).

Musculoskeletal system examination revealed sclerodactyly (Fig. 4), joint stiffness, tendon friction rubs, and knee joint crepitation.

The patient expressed Raynaud's phenomenon: severe pallor and cyanosis of the fingers on minimal contact with cold (Fig. 5).

X-ray of the hands (Fig. 6), showed evidence of calcinosis in soft tissues, osteolysis, and reduced joint spaces.

The patient's chief complaint remained swallowing difficulties and heartburn. On gastrointestinal (GI) exam, we saw sensitivity to palpation in the epigastric region, rumbling on palpation of the intestine. She had dysphagia and symptoms consistent with gastroesophageal reflux disease. The results of barium swallow esophagography (Fig. 7) showed that the GI motility was affected. The patient had achalasia cardia. She underwent fundoplication in November 2023 and subsequently also had 3 balloon dilations performed, which gave her temporary relief but each time, the symptoms would just keep recurring.

Laboratory tests revealed an ANA titer> 240 U/mL positive for centromere-B antibodies.

ISSN 2786-6661
eISSN 2786-667X

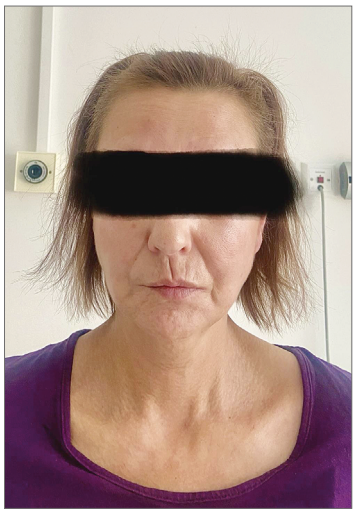

Figure 1. Hyperpigmentation, shiny mask-like face with purse-string mouth.

Figure 2. Cutaneous calcinosis on the middle ulnar part of the left forearm.

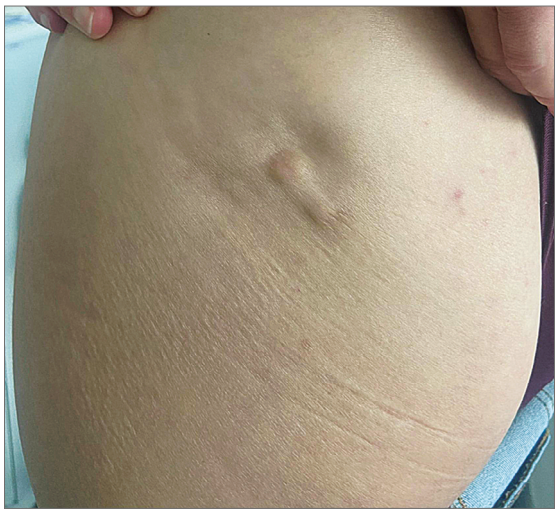

Figure 3. Cutaneous calcinosis on the right buttock.

Figure 4. Sclerodactyly, positive Prayer sign.

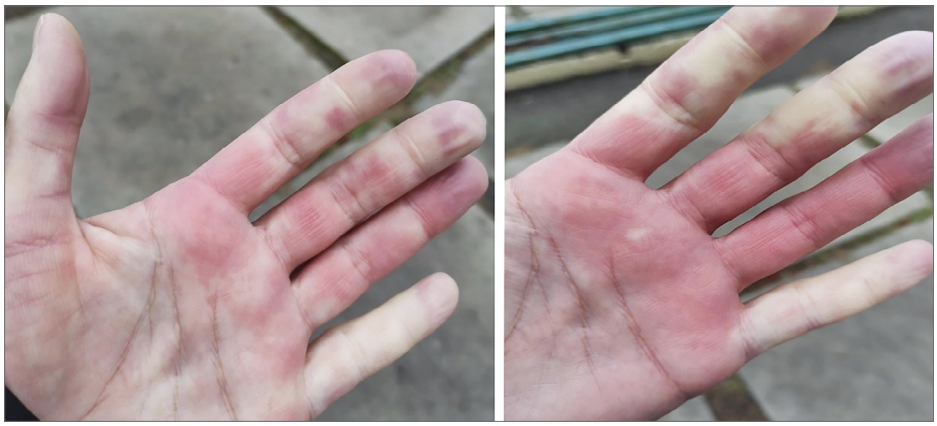

Figure 5. Raynaud's phenomenon- episodic whitening and blueness of fingers.

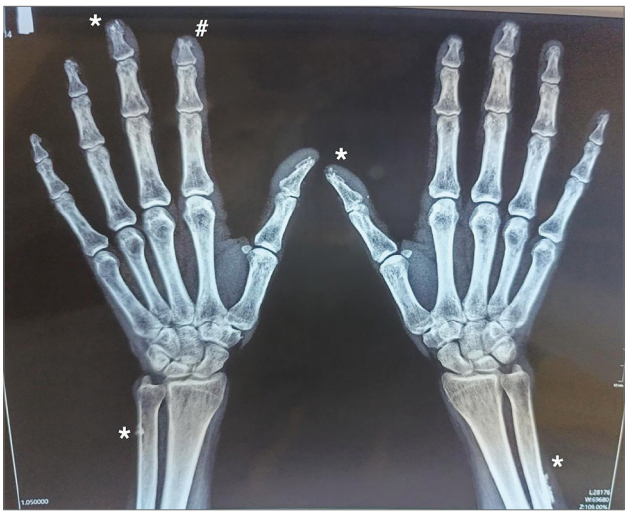

Figure 6. X-ray findings reduced joint spaces, distal osteolysis (#), and calcium phosphate deposition in soft tissue (*).

The tests for identifying other antibodies, like Scl-70 antibodies, RNA polymerase III antibodies, ANA-fibrillarin antibodies, and PM-Scl antibodies, were negative.

Nailfold capillaroscopy was performed, and it revealed a late scleroderma pattern, which is characterized by the presence of abnormal capillaries and a decrease in the density of capillaries.

According to the ACR/EULAR classification criteria, the patient had a score of 15, and thus the diagnosis was established in June 2024: ***Systemic Sclerosis, limited form, 2nd stage, active phase with skin involvement (cutaneous induration, mRSS 12, calcinosis, pitting scar), peripheral vessels (Raynaud's phenomenon), gastrointestinal tract (achalasia cardia, reflux***

ISSN 2786-6661
eISSN 2786-667X

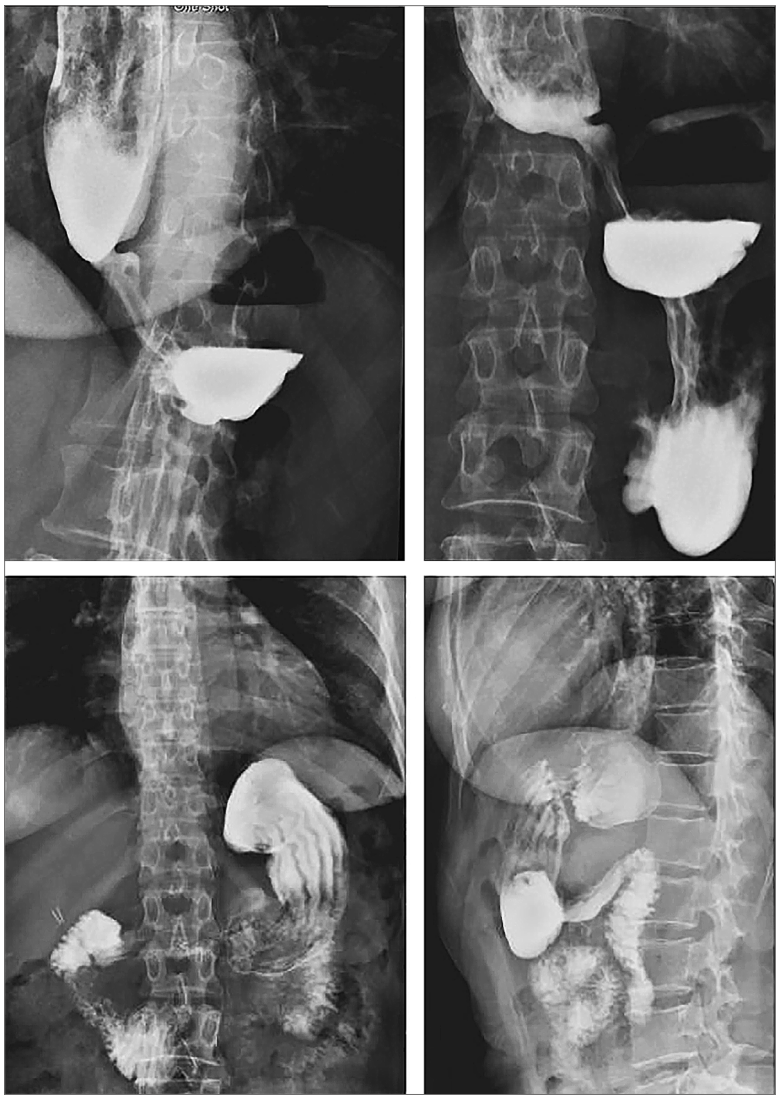

Figure 7. Barium swallow test (esophagography) showing oesophageal dilatation, achalasia with a distal tricture; dilated and atonic duodenum.

disease, erosive-ulcerative esophagitis), joints (sclerodactyly), Anticentromere B antibody positive. Concomitant Disease: Breast Cancer T2N0M0 (July 2022).

The treatment approach for this radiation-induced SSc was the same standard management used in idiopathic SSc. Initially, the patient was prescribed methotrexate 10 mg/week. Later on, in August and December 2024, the patient visited the hospital for follow-ups and evaluation of management. First, the methotrexate dose was increased to 25 mg/week and then it was adjusted at 20 mg/week and supplementary folic acid 10 mg/week. Also, she was started on nifedipine (retard form) 20 mg twice daily to keep Raynaud's phenomenon in check. Her GI symptoms were managed with omeprazole 20 mg/day, domperidone 10 mg twice daily and dietary recommendation. Supportive care and mild physical activity for joint mobility were suggested and she was advised to avoid cold exposure, caffeine and alcohol. The patient is having regular rheumatology and oncology follow-ups to date. The progression of the disease seems to be controlled with this treatment approach and the patient does not complain of any alarming exacerbations.

Discussion

The pathogenesis of radiation-induced SSc is not well-defined. The link between radiation exposure and SSc is hypothesized to involve microvascular endothelial injury: as

ISSN 2786-6661
eISSN 2786-667X

RT disrupts endothelial integrity, triggering chronic inflammation and fibroblast activation; autoimmune activation: there is increased antigen exposure post-radiation leading to autoantibody formation; fibrotic cascade: dysregulates TGF-β signaling and promotes excessive collagen deposition [1, 2]. These solitary links have not yet fit into a chain well enough to explain the entire pathophysiology behind such an occurrence. Only a handful of cases exist where RT preceded systemic autoimmune disease onset, suggesting a multifactorial interplay of genetics and environmental triggers [3, 4, 5]. We find a few similar clinical cases described in literature [5, 6]. In the case report by Dr. Nimbark, a 67-year-old woman developed systemic sclerosis following radiotherapy for cutaneous squamous cell carcinoma. Initial signs included localized morphoea within the irradiated field, which gradually progressed to generalized skin sclerosis and systemic features over two years. It discussed a potential for radiotherapy to trigger or exacerbate autoimmune fibrotic processes, supporting a possible link between radiation exposure and the pathogenesis of systemic sclerosis.

A 59-year-old woman undergoing neoadjuvant chemotherapy for HER2-positive breast cancer developed progressive skin fibrosis, initially localized to the irradiated area and subsequently spreading systemically ultimately leading to a diagnosis of SSc, supported by clinical features and positive autoantibody findings, including anti-Scl-70. Uniquely, her serologic evaluation revealed the presence of anti-RNA polymerase III antibodies, a marker often associated with malignancy-associated SSc. Despite discontinuation of cancer therapy, her fibrotic and systemic symptoms progressed, highlighting a potential radiation-induced autoimmune trigger and reinforcing the need for awareness of paraneoplastic SSc in oncologic care was described by Liu S et al [7].

While literature exists linking DNA damage from chemotherapy for breast cancer to fibrotic developments[4], our patient did not receive chemotherapy,she was treated exclusively with radiotherapy, making this explanation less likely in this context.

Most reported cases of post-radiation skin involve localized morphea rather than SSc. Studies point out the incidence of postirradiation morphea to be approximately 1 in 1000 breast cancer patients receiving radiotherapy, per year; while in the general population it is only 2.7 in 100,000 people [8, 9]. Morphea is a localized scleroderma variant marked by excessive collagen deposition causing skin and tissue fibrosis, without systemic involvement. Unlike systemic sclerosis which involves internal organs too, morphea primarily affects the skin but can cause significant cosmetic and functional impairment. Its cause is unclear, involving autoimmune and vascular factors, often triggered by trauma or radiotherapy. Postirradiation morphea is a rare subtype confined to the irradiated area, typically developing months to years after treatment.

This also arouses a need to develop new techniques to differentiate morphea from SSc, early on, because localised morphea, which is like a radiation-induced dermatologic reaction, generally occurring within the first 2 months of exposure, can be very similar to the skin changes occurring in the beginning with the development of SSc. In the initial stages, it may be very difficult to diagnose one from the other, but morphea mostly stays confined to the radiated field whereas SSc will evolve in a more generalized manner, affecting other organs gradually. Also, there can be an overlap of these symptoms with other cancer or radiation-related symptoms that may lead to a delay in the recognition and diagnosis of SSc. It is imperative to balance both rheumatological and oncological immunosuppressive therapies.

Conclusion

SSc is an extremely rare occurrence after RT, but it might have a long-term, life-altering effect. This case highlights the uncommon but significant occurrence of SSc following RT. Very few similar cases have been reported in the literature, and all of them emphasize that early diagnosis and a multidisciplinary approach are essential to optimizing outcomes. The diagnostic dilemma between post-irradiation morphea and SSc demands that physicians be highly vigilant in monitoring the patient's symptoms for early intervention. This is essential for effective

ISSN 2786-6661
eISSN 2786-667X

symptom management, as early detection can help slow disease progression, give patients a chance at a better and unrestricted quality of life, and also prevent potential complications. Oncologists and rheumatologists should monitor breast cancer survivors for post-radiation autoimmune manifestations. Future research should focus on identifying at-risk populations, exploring the genetic predisposition for radiation-induced autoimmunity, and clarifying its underlying mechanisms. This case is unique, as there are nominal reports on generalised morphoea converting to SSc post-radiotherapy.

Limitation

In the discussion, we compared our patient case with a limited number of similar reports identified through a PubMed search restricted to freely available and published in English. This approach may have inadvertently excluded relevant studies indexed in other databases such as Web of Science or Scopus, as well as studies published in other non-English languages.

Ethical Disclosures

Informed written consent was obtained from the patient for the publication of this case report and the accompanying images. Our observation was descriptive in nature and did not include any interventions.

Financing

This research did not receive external funding.

Conflict of interests

This publication does not cause any conflict between the authors, has not been and will not be the subject of commercial interest or remuneration in any form.

Consent to publication

All authors have read the text of the article and gave consent to its publication

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Ukrainian Scientific Medical Youth Journal
Issue 2 (154), 2025
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ISSN 2786-6661
eISSN 2786-667X

Клінічний випадок системної склеродермії, яка індукована променевою терапією у пацієнтки з раком молочної залози

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Анотація.Системна *склеродермія — це рідкісне системне захворювання сполучної тканини, що характеризується прогресуючим фіброзом, судинною дисфункцією та імунною дисрегуляцією, що супроводжується формуванням аутоантитіл до тканин власного організму. У той час як локалізований фіброз шкіри, відомий як морфея, є визнаним ускладненням променевої терапії, розвиток системної склеродермії після опромінення залишається надзвичайно рідкісним явищем. Цей випадок описує початок системної склеродермії у хворої на рак молочної залози після отримання ад'ювантної променевої терапії, наголошуючи на складності раннього розпізнавання та лікування. У п'ятдесятирічної жінки без аутоімунного захворювання в анамнезі виявили прогресуюче ущільнення шкіри, феномен Рейно, скутість суглобів і труднощі з ковтанням через кілька місяців після завершення променевої терапії з приводу раку молочної залози. Діагностичне дослідження виявило позитивні антитіла до центромеру B, кальциноз м'яких тканин і порушення моторики стравоходу. На підставі ACR/EULAR, 2013 критеріїв, підтверджено діагноз системної склеродермії. Пацієнтці було розпочато імуносупресивну терапію, вазодилататори та терапію шлунково-кишкової дисфункції, що призвело до часткового симптоматичного покращення. Патофізіологія радіаційно-індукованої системної склеродермії не вивчена остаточно, але вважається, що може включати мікроваскулярне ендотеліальне пошкодження, імунну дисрегуляцію та активацію фібробластів. Існуючі дані свідчать про те, що променева терапія може діяти як тригерний фактор у генетично схильних осіб, що призводить до посилення латентних аутоімунних процесів. Враховуючи все більш широке використання променевої терапії в онкології, важливо усвідомлювати її потенційні віддалені наслідки. Мультидисциплінарний підхід із залученням ревматологів, онкологів та допоміжного персоналу має важливе значення для оптимізації результатів. Раннє втручання та цілеспрямоване лікування може зменшити прогресування захворювання та покращити якість життя. Необхідні подальші дослідження, щоб з'ясувати механізми, що лежать в основі системної склеродермії, яка індукована радіацією, оцінити потенційні фактори ризику та розробити профілактичні стратегії. Виявлення імунних змін, пов'язаних із пострадіаційним фіброзом, може сприяти персоналізованим підходам до скринінгу та раннього втручання для осіб, які проходять променеву терапію. Підвищення обізнаності про це рідкісне, але серйозне ускладнення сприятиме ранній діагностиці та своєчасному лікуванню та покращенню прогнозу пацієнтів.*

Ключові слова: рак молочної залози, променева терапія, системна склеродермія.