Cureus
Part of SPRINGER NATURE

Open Access Case Report

Paraneoplastic Systemic Sclerosis Associated With High-Grade Serous Ovarian Carcinoma: A Case Report

Review began 09/28/2026
Review ended 11/09/2026
Published 11/19/2026

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DOI: 10.7759/cureus.119943

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Abstract

Unlike dermatomyositis, which is widely linked to malignancy, systemic sclerosis is rarely recognized as a paraneoplastic condition in everyday practice, largely due to a lack of clinical awareness regarding this emerging concept. However, mounting pathophysiological and epidemiological data suggest that systemic sclerosis may represent a putative paraneoplastic syndrome, particularly in the anti-RNA polymerase III-positive subset.

We report the case of a 58-year-old female who, one month after being diagnosed with metastatic high-grade serous ovarian carcinoma (FIGO stage IIIC), developed Raynaud's phenomenon, which rapidly progressed over the following four months to sclerodactyly, cutaneous sclerosis of the dorsum of both hands and forearms, facial telangiectasias, and microstomia. Nailfold capillaroscopy demonstrated devascularization and mild capillary ectasia. Laboratory evaluation demonstrated a positive antinuclear antibody (ANA) titer (1:640) with a fine speckled nuclear pattern and high-titer anti-RNA polymerase III (anti-RNAP III) antibodies (212 U/mL), the autoantibody most strongly linked to paraneoplastic systemic sclerosis. The patient fulfilled 17 points on the 2013 ACR/EULAR classification criteria for systemic sclerosis. She underwent neoadjuvant chemotherapy, cytoreductive surgery, and maintenance therapy with niraparib. Following antineoplastic treatment, the patient experienced clinically significant improvement in cutaneous sclerosis without evidence of pulmonary or renal progression of systemic sclerosis.

This report describes an unusual presentation of paraneoplastic systemic sclerosis associated with high-grade serous ovarian carcinoma, an uncommon association, as breast and lung cancers are the malignancies most frequently linked to systemic sclerosis. Furthermore, it reinforces the necessity of maintaining a high index of suspicion for underlying occult malignancies in patients presenting with recent-onset systemic sclerosis and anti-RNAP III positivity.

Categories: Rheumatology, Oncology, Internal Medicine
Keywords: anti-rna polymerase iii antibody, high-grade serous ovarian cancer, ovarian cancer, paraneoplastic syndrome, systemic sclerosis

Introduction

Systemic sclerosis (SSc) is a complex systemic autoimmune disease characterized by microvascular injury, immune dysregulation, and progressive fibrosis affecting the skin and internal organs. The clinical spectrum is highly heterogeneous, encompassing
cutaneous, vascular, gastrointestinal, pulmonary, cardiac, and renal involvement. Diagnostic classification relies on a combination of clinical, laboratory, and serological findings, with Raynaud's
phenomenon, sclerodactyly, telangiectasias, and disease-specific autoantibodies serving as diagnostic pillars [1,2].

The association between SSc and malignancy is increasingly recognized as a bidirectional relationship. On one hand, long-standing SSc creates a chronic inflammatory and fibrotic microenvironment that elevates the baseline risk of secondary somatic malignancies [3]. On the other hand, an occult tumor can directly trigger a paraneoplastic autoimmune response, where the occult malignancy is hypothesized to act as the primary inciting trigger for new-onset SSc [3,4]. This bidirectional mechanism is particularly prominent in patients harboring anti-RNA polymerase III (anti-RNAP III) autoantibodies [4,5].

In clinical practice, new-onset SSc in older individuals, especially when accompanied by anti-RNAP III positivity, must be interpreted as a critical "red flag" for an underlying occult malignancy. Observational cohorts demonstrate that anti-RNAP III positivity carries a remarkably high risk for synchronous cancer diagnosis around SSc onset; thus, while age- and sex-appropriate routine cancer screening remains foundational, high-risk SSc presentations warrant an individualized, enhanced diagnostic oncological

evaluation [5,6]. While the link between anti-RNAP III positivity and malignancies such as breast and lung carcinomas is well established, less common entities like High-Grade Serous Ovarian Carcinoma (HGSOC) are increasingly recognized as potential, albeit less frequent, tumor-specific triggers. Characterized by marked genomic instability and universal *TP53* mutations, HGSOC is hypothesized to provide a fertile substrate for tumor-derived neoantigens [7]. Consequently, incorporating targeted pelvic and gynecological evaluation may be considered alongside standard screening when assessing older females presenting with rapid-onset SSc and high-risk serological profiles [5,7].

The pathophysiological rationale for paraneoplastic SSc centers on somatic alterations within the *POLR3A* gene in tumor cells. These genetic alterations yield mutated RNA polymerase III subunits that act as neoantigens, triggering a host immune response that cross-reacts with wild-type RNA polymerase III in normal microvascular and dermal tissues [8]. Recognizing this paraneoplastic etiology holds profound therapeutic implications, as effective cancer management can lead to regression of autoimmune manifestations. Here, we present the case of a 58-year-old woman with new-onset SSc and high-titer anti-RNAP III positivity following a diagnosis of metastatic HGSOC (FIGO stage IIIC) [9], who experienced marked cutaneous improvement (modified Rodnan skin score [10] reduction from 10 to 4) following antineoplastic therapy. This case underscores the crucial role of a multidisciplinary approach involving rheumatologists, oncologists, and gynecologic oncologists in managing suspected cancer-associated autoimmunity.

Case Presentation

A 58-year-old female with no prior history of autoimmune disease, smoking, or alcohol consumption was admitted to the hospital on Day 1 (D1: March, 2025), presenting with a 12-month history of unintentional weight loss of 20 kg (from 71 kg to 51 kg) and high-volume ascites. Abdominal and pelvic computed tomography (CT) performed upon admission demonstrated marked diffuse pelvic peritoneal thickening (Figure *1*), pronounced nodular thickening of the greater omentum in the periumbilical region, and moderate-to-large volume ascites (Figure *2*). During this inpatient admission, a comprehensive oncogynecological investigation-including diagnostic paracentesis, diagnostic laparoscopy, and peritoneal biopsy-confirmed metastatic high-grade serous carcinoma of tubo-ovarian origin, classified as FIGO stage IIIC [9], testing negative for *BRCA1* and *BRCA2* mutations (*BRCA1/2* wild-type).

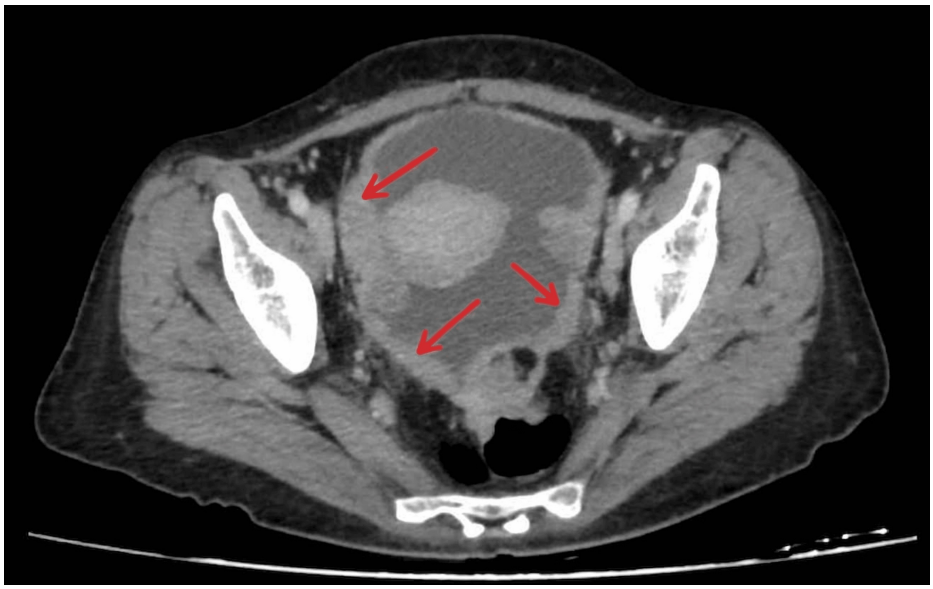


FIGURE 1: Pelvic computed tomography at initial cancer diagnosis.

Axial contrast-enhanced computed tomography scan of the pelvis demonstrating marked diffuse pelvic peritoneal thickening and nodular implants (indicated by red arrows), characteristic of peritoneal carcinomatosis.



FIGURE 2: Abdominal computed tomography at initial cancer diagnosis.

Axial contrast-enhanced computed tomography scan of the abdomen showing pronounced nodular thickening of the greater omentum in contact with the periumbilical region (indicated by the red arrow) accompanied by moderate-to-large volume ascites (indicated by the green arrow).

On Day 30 (D30), during an outpatient oncology follow-up consultation, the patient reported the recent onset of bilateral Raynaud's phenomenon in both hands and feet, associated with rapidly progressive diffuse skin thickening [11]. Prompted by these clinical features, the attending oncologist ordered an initial immunological workup on D30, which revealed a positive antinuclear antibody (ANA) titer of 1:640 with a fine speckled nuclear pattern and markedly elevated anti-RNA polymerase III (anti-RNAP III) autoantibody levels at 212 U/mL (reference: <20 U/mL). Anti-Scl-70, anti-Ro/SSA, anti-La/SSB, and rheumatoid factor were all negative. Erythrocyte sedimentation rate (ESR) was elevated at 74 mm/hour.

On Day 38 (D38: April, 2025), neoadjuvant chemotherapy with six cycles of carboplatin and paclitaxel was initiated, achieving a partial radiological response with resolution of ascites and reduction of peritoneal implants.

On Day 90 (D90) (three months post-diagnosis), formal rheumatological physical examination revealed sclerodactyly, cutaneous sclerosis on the dorsum of both hands and forearms, facial telangiectasias, mild microstomia, and an initial modified Rodnan skin score (mRSS) of 10 [10], without active digital ulcers. Nailfold capillaroscopy performed on D90 demonstrated devascularization and mild capillary ectasia, characteristic of a non-specific microangiopathy pattern (Figure *3*).

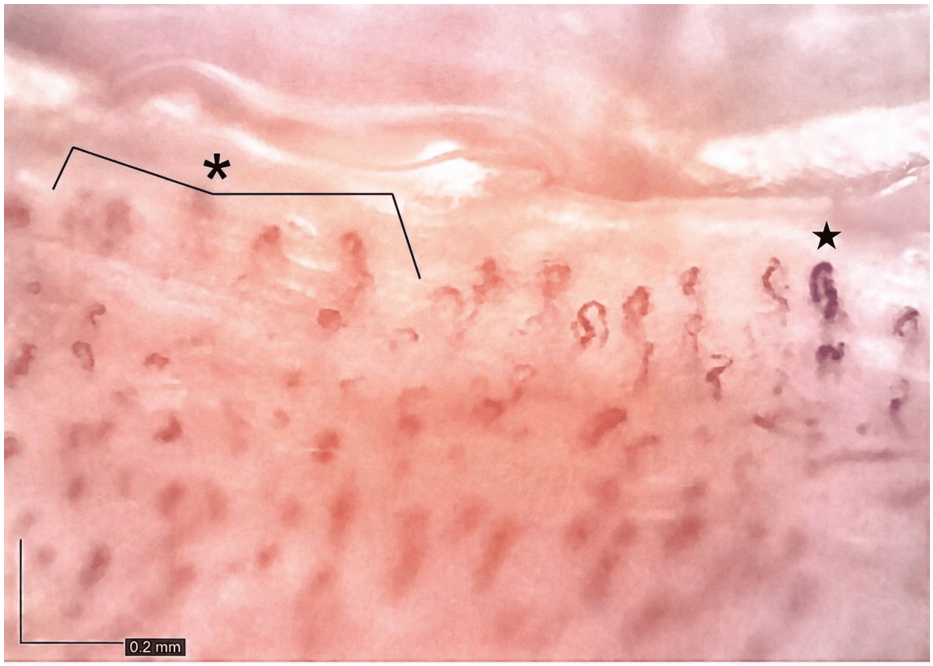


FIGURE 3: Nailfold capillaroscopy.

Nailfold capillaroscopy demonstrating capillary ectasia (indicated by the star, ★) and a focal area of capillary loss/devascularization (indicated by the bracket and asterisk, *), characteristic of a non-specific microangiopathy pattern.

The patient fulfilled the 2013 ACR/EULAR classification criteria for SSc with a total score of 17 points: skin thickening proximal to the metacarpophalangeal joints (9 points), Raynaud's phenomenon (3 points), telangiectasias (2 points), and anti-RNAP III autoantibody positivity (3 points), well above the classification threshold of 9 points [1].

Additionally, scleroderma mimics and SSc-like disorders, such as nephrogenic systemic fibrosis, scleroderma diabeticorum, scleromyxedema, erythromelalgia, porphyria cutanea tarda, lichen sclerosus, graft-versus-host disease, and diabetic cheiroarthropathy, were systematically ruled out. Diabetic manifestations (scleroderma diabeticorum and diabetic cheiroarthropathy) were excluded as the patient was non-diabetic with normal baseline fasting glucose levels (Table *1*). Nephrogenic systemic fibrosis was rendered highly unlikely due to preserved baseline renal function, despite having undergone abdominal and pelvic magnetic resonance imaging with modern macrocyclic gadolinium-based contrast media. Viral serologies for hepatitis B, hepatitis C, and HIV were negative. Graft-versus-host disease was definitively excluded by the complete lack of a history of hematopoietic stem cell or solid organ transplantation. Crucially, all these mimics characteristically lack Raynaud's phenomenon, SSc-specific autoantibodies (anti-RNAP III), characteristic capillaroscopic microangiopathy, and typical acral cutaneous involvement, as presented in this case.

Parameter	Patient Result	Reference Range	Units
ANA	1:640 (nuclear fine speckled pattern)	< 1:80	Titer
Anti-RNAP III	212	< 20	U/mL
Anti-Scl-70	Negative	Negative	N/A
Anti-Ro/SSA	Negative	Negative	N/A
Anti-La/SSB	Negative	Negative	N/A
Rheumatoid Factor	< 20	< 20	IU/mL
HBsAg	Negative	Negative	N/A
Anti-HBs	Negative	Negative	N/A
Anti-HBc Total	Negative	Negative	N/A

Anti-HIV 1/2	Negative	Negative	N/A
Treponemal Test (Syphilis)	Negative	Negative	N/A
Hemoglobin	9.6	12.0–15.5	g/dL
Leukocytes	7,220	4,000–11,000	/mm³
Neutrophils	5,833.8	1,800–7,700	/mm³
Lymphocytes	750.9	1,000–4,800	/mm³
Platelets (baseline)	328,000	150,000–400,000	/mm³
INR	1.19	0.8–1.2	Ratio
ESR	74	2–30	mm/h
C-Reactive Protein (CRP)	8.69	< 0.50	mg/dL
CA-125	587.4	< 35.0	U/mL
CA 19-9	7.99	< 37.00	U/mL
CEA	0.91	< 5.00	ng/mL
Alpha-Fetoprotein (AFP)	< 2.00	0.89–8.78	ng/mL
Beta-hCG	3.41	< 5.00	mIU/mL
BRCA1/2 Mutations	Negative (*BRCA1/2* wild-type)	Negative (wild-type)	N/A
Fasting Plasma Glucose	94	70–99	mg/dL
Glycated Hemoglobin (HbA1c)	5.3	< 5.7	%
Creatinine	0.83	0.60–1.10	mg/dL
Urea	33	15–45	mg/dL
Sodium	142	135–145	mEq/L
Potassium	4.6	3.5–5.1	mEq/L
Serum Albumin	2.6	3.5–5.2	g/dL
AST	17	< 35	U/L
ALT	11	< 35	U/L
GGT	34	< 38	U/L
Alkaline Phosphatase	107	35–104	U/L
Total Bilirubin	0.28	0.20–1.20	mg/dL
Direct Bilirubin	0.18	< 0.30	mg/dL
Urinalysis	Normal / Unremarkable	Normal	N/A

TABLE 1: Baseline laboratory and immunological investigations.

ANA: antinuclear antibody; Anti-RNAP III: anti-RNA polymerase III antibody; Anti-Scl-70: anti-topoisomerase I antibody; Anti-Ro: anti-SSA/Ro antibody; Anti-La: anti-SSB/La antibody; HBsAg: hepatitis B surface antigen; Anti-HBs: hepatitis B surface antibody; Anti-HBc: hepatitis B core antibody; HIV: human immunodeficiency virus; BRCA1/2: breast cancer gene 1/2; CA-125: cancer antigen 125; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; AFP: alpha-fetoprotein; Beta-hCG: beta-human chorionic gonadotropin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HbA1c: glycated hemoglobin; INR: international normalized ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; N/A: not applicable.

On Day 210 (D210) (seven months post-diagnosis), she underwent optimal cytoreductive surgery consisting of omentectomy, bilateral salpingo-oophorectomy (Figure *4*, *5*), and complete resection of visible peritoneal implants.

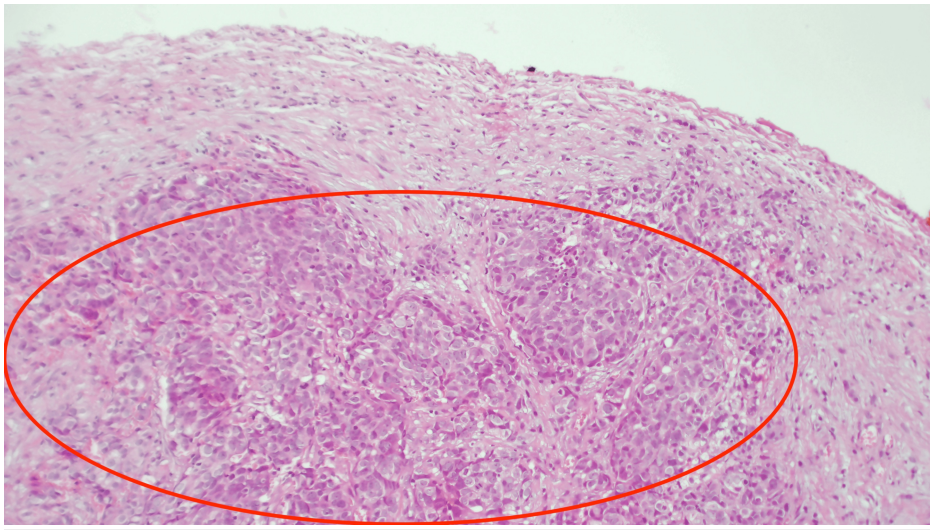


FIGURE 4: Histopathological evaluation of the ovary.

Photomicrograph of the ovarian tissue (H&E stain, 100x magnification). The area outlined within the red circle demonstrates neoplastic tumor tissue exhibiting a solid growth pattern, significant nuclear pleomorphism, and marked atypia, surrounded by residual non-neoplastic ovarian parenchyma.

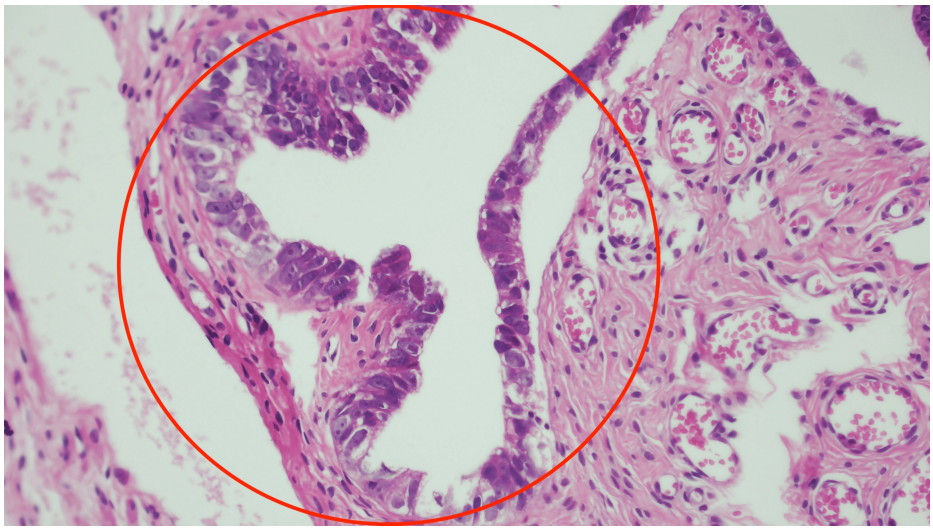


FIGURE 5: Histopathological evaluation of the fallopian tube.

Photomicrograph of the fallopian tube (H&E stain, 400x magnification). The epithelium outlined within the red circle represents high-grade neoplastic tissue, characterized by severe nuclear atypia, marked pleomorphism, hyperchromasia, an intraepithelial growth pattern, and complete loss of cellular polarity.

On Day 270 (D270) (nine months after initial diagnosis / two months postoperatively), maintenance therapy with oral niraparib (200 mg/day) was initiated. Three weeks into maintenance therapy, on Day 291 (D291), she developed severe grade 4 thrombocytopenia with a platelet nadir of 18,000/mm^3 complicated by hematemesis, prompting immediate and permanent drug discontinuation. The patient declined esophagogastroduodenoscopy during hospitalization. Although these upper gastrointestinal symptoms raised suspicion for SSc-related esophageal involvement, they were heavily confounded by active peritoneal carcinomatosis and chemotherapy toxicity; because the patient declined esophagogastroduodenoscopy, esophageal involvement could neither be definitively confirmed nor ruled out.

On Day 330 (D330) (11 months post-diagnosis), disease progression was identified by rising tumor markers. Carboplatin and paclitaxel were reintroduced but discontinued by the patient after three cycles due to poor treatment tolerance. On Day 450 (D450) (15 months post-diagnosis), a trial of oral cyclophosphamide was attempted but quickly suspended due to refractory nausea and vomiting. Throughout

follow-up, serum creatinine fluctuated between 0.71 and 1.18 mg/dL, which improved following intravenous hydration, without severe arterial hypertension or evidence of microangiopathic hemolytic anemia.

On Day 480 (D480) (16 months post-diagnosis), she was admitted with severe colicky abdominal pain and vomiting. Abdominal computed tomography demonstrated retroperitoneal para-aortic lymphadenopathy, nodular peritoneal thickening, loculated ascites, and bowel subocclusion resulting from peritoneal carcinomatosis.

Despite these oncological complications and clinical challenges, antineoplastic treatment resulted in marked cutaneous improvement, with the modified Rodnan skin score (mRSS) decreasing from 10 to 4 (Figures *6*, *7*). At presentation (D90), the initial score of 10 comprised moderate sclerodactyly (2 points bilaterally), moderate skin thickening on the dorsum of both hands (2 points bilaterally), and mild involvement of both forearms (1 point bilaterally). Following antineoplastic therapy, the residual score of 4 reflected mild sclerodactyly (1 point bilaterally) and mild dorsal hand skin thickening (1 point bilaterally), alongside complete resolution of forearm involvement, with no progression to renal, pulmonary, or cardiac involvement.

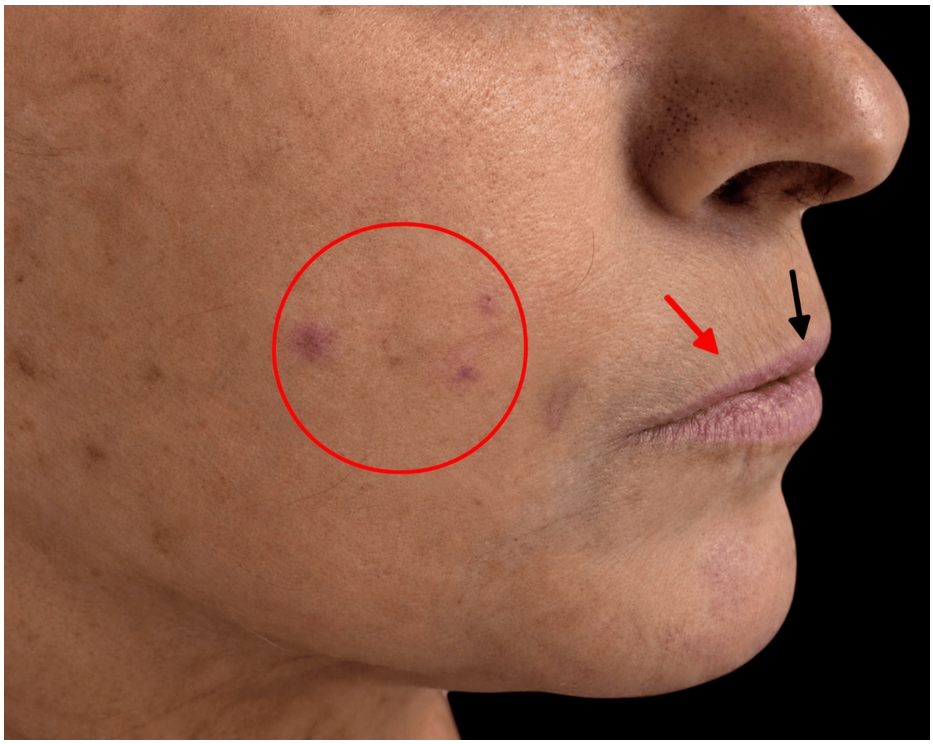


FIGURE 6: Facial clinical features following antineoplastic therapy.

Follow-up clinical photograph demonstrating partial cutaneous response post-treatment. Residual facial telangiectasias are highlighted within the red circle; lip thinning is indicated by the black arrow; and subtle perioral radial furrowing associated with microstomia is indicated by the red arrow.

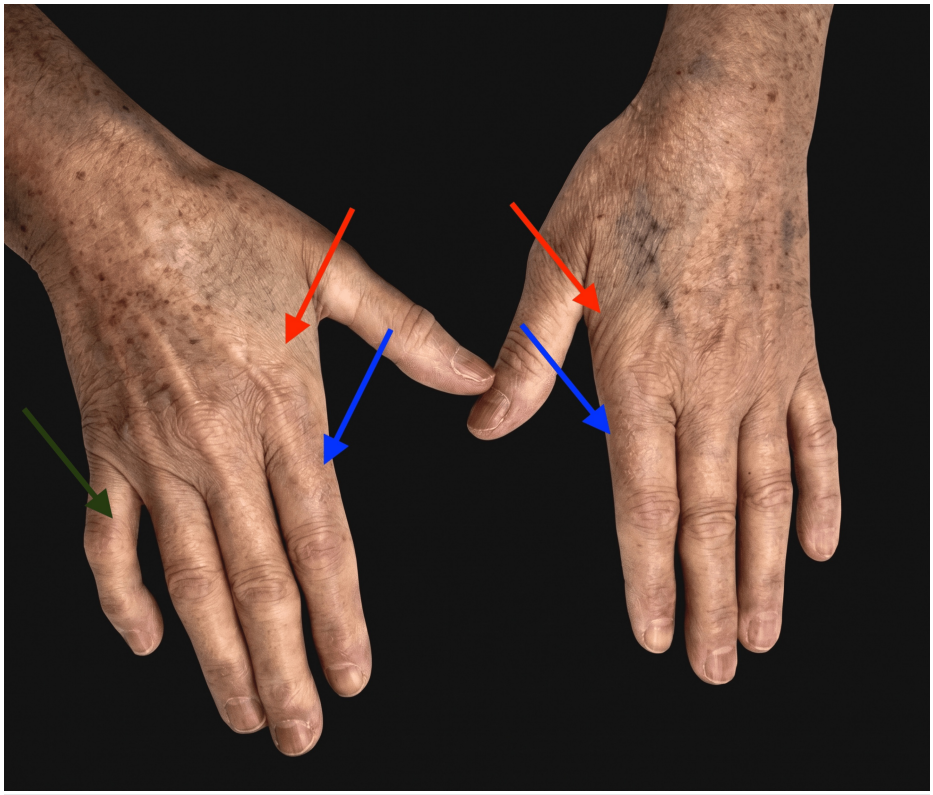


FIGURE 7: Cutaneous changes of the hands following antineoplastic therapy.

Photograph demonstrating partial cutaneous response post-treatment (overall modified Rodnan skin score reduction from 10 to 4). Persistent skin thickening on the dorsum of both hands is indicated by the red arrows; residual mild sclerodactyly is indicated by the blue arrow; and a fixed flexion contracture of the fifth digit secondary to cutaneous sclerosis is indicated by the green arrow.

Discussion

The bidirectional relationship and anti-RNAP III as a red flag

The coexistence of new-onset SSc, high-titer anti-RNAP III antibodies, and high-grade serous ovarian carcinoma illustrates the complex bidirectional relationship between autoimmunity and oncogenesis. While SSc-associated chronic tissue damage and chronic immune activation predispose patients to long-term cancer development, a tumor-induced paraneoplastic syndrome represents the inverse paradigm: the malignancy is presumed to serve as the initial biological trigger for autoimmune manifestations [3].

Large-scale epidemiological data, such as the EULAR Scleroderma Trials and Research (EUSTAR) cohort analysis by Lazzaroni et al., strongly reinforce anti-RNAP III positivity as an alarming red flag for synchronous occult cancer [5]. Patients with anti-RNAP III antibodies exhibit a markedly increased risk of concomitant malignancy at SSc onset compared to anti-RNAP III-negative controls. This clustering is strictly temporal, concentrated within a narrow window extending from 6 months before to 12 months after SSc diagnosis (OR 7.38, 95% CI 1.61-33.8, 7.0% vs. 1.0%, $p = 0.004$) and up to 2 years before and after SSc onset (OR 3.85, 95% CI 1.36-10.9, 9.0% vs. 2.5%, $p = 0.007$). Crucially, the risk of cancer is not statistically elevated beyond 2 years post-SSc diagnosis (9.0% vs. 6.5%, $p = 0.423$), emphasizing that new-onset SSc represents the key temporal window for paraneoplastic presentation. Furthermore, among anti-RNAP III-positive patients, those with concomitant malignancies are significantly older at SSc onset compared to those without cancer (mean age 65.3 vs. 49.3 years, $p < 0.001$). This age discrepancy may be partly explained by immunosenescence and age-related impairment of tumor immune surveillance [12]. In younger individuals, a robust immune system efficiently identifies and clears occult mutated cells before overt clinical malignancy develops. Conversely, in older patients, immunosenescence permits tumor immune evasion and persistent exposure to tumor-derived neoantigens, providing the chronic antigenic stimulus required to trigger cross-reactive paraneoplastic autoimmunity. In our 58-year-old patient, the acute emergence of Raynaud's phenomenon and rapid progression to sclerodactyly within one month of an advanced HGSOC diagnosis perfectly fits this high-risk demographic profile, warranting urgent, targeted oncological investigation.

Although anti-RNAP III autoantibodies represent the strongest and most extensively validated serological marker of paraneoplastic SSc, other distinct autoantibody subsets have also been identified in cancer-associated scleroderma. Notably, anti-RNPC3 autoantibodies (targeting a core component of the minor spliceosome complex) have been recognized as an independent risk factor for synchronous cancer in SSc patients [13]. Additionally, isolated (monospecific) anti-Ro52 autoantibodies have recently emerged as a distinct serological predictor for cancer-associated systemic sclerosis [14].

Immunogenic profile of HGSOC and gynecologic screening

Although breast and lung carcinomas are the malignancies most commonly linked to paraneoplastic SSc, gynecologic malignancies, specifically HGSOC, hold unique pathophysiological relevance. HGSOC is defined by pervasive genomic instability, universal *TP53* mutations, and extensive copy-number alterations, rendering it a highly immunogenic tumor capable of generating diverse neoepitopes [7]. Despite its lower overall incidence compared to breast cancer, the strong antigenic potential of HGSOC makes it a potent driver of cross-reactive autoimmunity. Given that early-stage ovarian cancers are notoriously asymptomatic, these findings underscore the imperative to include pelvic ultrasonography, cross-sectional abdominal/pelvic imaging, and serum CA-125 measurement in the standardized diagnostic screening protocol for older women presenting with new-onset, anti-RNAP III-positive SSc [5,7].

The *POLR3A* mechanistic axis

The molecular cornerstone of paraneoplastic SSc involves somatic mutations or gene copy-number alterations within the *POLR3A* locus inside tumor cells, as demonstrated by Joseph et al. [8]. Tumor-specific genetic alterations in *POLR3A* give rise to altered RNA polymerase III peptides. These neoantigens are processed and presented by host antigen-presenting cells, breaching immune tolerance and driving both humoral (autoantibody production) and cell-mediated immune responses. Because these autoantibodies cross-react with wild-type RNA polymerase III ubiquitously expressed in human dermal fibroblasts and endothelial cells, an autoimmune cascade is initiated, manifesting clinically as microvascular obliteration and rapid dermal skin thickening [8].

Comparison with literature and response to therapy

Our case aligns with similar paraneoplastic SSc literature, such as reports by Monfort et al. and Taieb et al., where patients with ovarian and lung malignancies experienced objective regression of cutaneous sclerosis following primary surgical resection or systemic chemotherapy [15,16]. In our patient, antineoplastic treatment (neoadjuvant carboplatin/paclitaxel and cytoreductive surgery) led to a significant clinical response, evidenced by a drop in the modified Rodnan skin score (mRSS) from 10 to 4 without the addition of heavy conventional immunosuppressive agents. The resolution of skin sclerosis in parallel with tumor cytoreduction supports a putative paraneoplastic association rather than a coincidental finding, although definitive causality cannot be established in a single-case report [15-18].

Anti-RNAP III antibodies are also strongly linked to scleroderma renal crisis (SRC) [19]. In our patient, although serum creatinine fluctuated between 0.71 and 1.18 mg/dL, the absence of refractory hypertension, microangiopathic hemolytic anemia, or flash pulmonary edema ruled out SRC. These transient creatinine shifts were clinically attributed to volume depletion, chemotherapy-induced nephrotoxicity, and advanced peritoneal carcinomatosis.

Multidisciplinary management and clinical challenges

Managing paraneoplastic SSc requires tight, continuous collaboration across a multidisciplinary team comprising rheumatology, medical oncology, and gynecologic oncology. A central clinical challenge lies in navigating overlapping treatment toxicities and therapeutic dilemmas. Standard immunosuppressive therapy for progressive SSc (such as cyclophosphamide or mycophenolate mofetil) carries substantial hematologic and infectious risks when administered concurrently with combination platinum-based chemotherapy. Conversely, novel targeted oncological agents can induce severe autoimmune-like side effects or hematologic cytopenias. In our patient, maintenance therapy with niraparib (a PARP inhibitor) caused profound grade 4 thrombocytopenia (nadir 18,000/mm^3) complicated by upper gastrointestinal bleeding, necessitating immediate drug cessation [20]. This event highlights the necessity of integrated co-management to balance oncological efficacy against drug toxicity, keeping tumor control as the primary driver for achieving SSc remission.

Limitations

Limitations of this report include its single-case design, the absence of somatic tumor sequencing to definitively verify *POLR3A* mutations in the ovarian tissue, and the inability to perform an esophagogastroduodenoscopy (due to patient refusal) to definitively differentiate SSc-related esophageal dysmotility from chemotherapy-induced mucositis and peritoneal carcinomatosis. Additionally, the natural history of systemic sclerosis characteristically includes a potential phase of spontaneous skin softening over time. Although the rapid temporal coupling between antineoplastic therapy and skin score reduction strongly suggests a tumor-driven process, spontaneous disease trajectory remains a potential confounding

factor that cannot be entirely ruled out.

Conclusions

This report highlights that SSc can manifest as a paraneoplastic syndrome associated with anti-RNA polymerase III (anti-RNAP III) autoantibodies, a process widely proposed in the literature to be mediated by cross-reactive immune responses against tumor-derived *POLR3A* neoepitopes. Crucially, this case reminds clinicians that while patients with established SSc carry an increased risk of developing secondary malignancies, new-onset SSc may also emerge as a potential paraneoplastic manifestation unmasking an occult malignancy, in this instance, high-grade serous ovarian carcinoma. Recognizing this bidirectional relationship and maintaining a high index of suspicion in new-onset anti-RNAP III-positive SSc is essential for prompt diagnostic workup, timely oncologic intervention, and coordinated multidisciplinary care.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Hospital de Clínicas da Universidade Federal do Paraná issued approval 6.060.736. In view of the above, the Human Research Ethics Committee of the HC-UFPR, in accordance with the duties defined in CNS Resolution Number 466/2012 and CNS Operational Standard Number 001/2013, hereby approves the project as proposed for the initiation of the research. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

During the preparation of this manuscript, the authors utilized Google Gemini for language translation into English, grammatical polishing, and manuscript structural formatting assistance. Following the use of this tool, all authors reviewed, critically verified, and edited the final text to ensure medical accuracy, factual integrity, and adherence to editorial standards. The authors take full and public responsibility for the intellectual content, integrity, and findings presented in this work.

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