Cancer and Scleroderma

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KEYWORDS

• Scleroderma • Malignancy • Autoantibodies • Epidemiology • Cancer screening

KEY POINTS

- Scleroderma may be a paraneoplastic phenomenon in unique patient subgroups, including those with anti-RNA polymerase III antibodies or those who are negative for centromere, topoisomerase 1, or RNA polymerase III antibodies.
- All patients with new-onset scleroderma should undergo comprehensive physical examination and age-based, sex-based, and risk factor–based cancer screening tests.
- Recent data suggest that autoantibody and cutaneous subtype may define cancer risk, type, and timing in scleroderma. If validated, these findings may inform the development of targeted cancer screening guidelines.

EPIDEMIOLOGY OF CANCER IN PATIENTS WITH SCLERODERMA

Most epidemiologic studies have shown that individuals with scleroderma have an increased age-adjusted and sex-adjusted risk of developing cancer, with this risk generally ranging from 1.5 to 4 times higher than that of the general population.[1–14] Although it is beyond the scope of this article to discuss all of these studies, particular attention is drawn to 3 meta-analyses that have both quantified the magnitude of cancer risk and examined the particular tumor types that are enriched in scleroderma.

Onishi and colleagues[9] examined 6 population-based cohort studies comprising a total of 6641 people with scleroderma from Australia, northern Europe, Taiwan, and the United States. They found a pooled standardized incidence ratio (SIR) of 1.41 for cancer overall, with a trend toward a greater risk in men than women (SIR, 1.85 vs 1.33 respectively). With regard to particular tumors types that were enriched in these cohorts, they found an increased risk of lung, liver, and hematologic cancers overall, as well as an increased risk of bladder cancer in women and nonmelanomatous skin cancer in men. In contrast, there was no increased risk of breast cancer,

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although the investigators excluded cases of cancer that were diagnosed before the onset of scleroderma. The temporal clustering of breast cancer and scleroderma, with either diagnosis arising shortly before the other, has been well described in the literature and is discussed in more detail later.[15–18] They likewise did not find an increased risk of other sex-specific cancers such as prostate, cervical, or uterine cancer. A contemporaneous meta-analysis by Zhang and colleagues[14] found similar results, with increased SIRs for lung cancer, hematopoietic cancer, and non-Hodgkin lymphoma, but not breast cancer.

Bonifazi and colleagues[2] conducted the largest meta-analysis to date using 16 observational studies, which included most of the articles examined by Onishi and colleagues[9] and Zhang and colleagues[14] as mentioned earlier. Compared with the general population, the relative risk (RR) of cancer in scleroderma was 1.75, with particularly strong associations between scleroderma and lung cancer (RR, 4.35) and hematologic neoplasms (RR, 2.24). Of the included studies assessing liver cancer or esophageal cancer, all showed an increased risk, with SIRs ranging from 3.30 to 7.35 and 2.86 to 35.0, respectively. Available data for the incidence of stomach, pancreas, skin, and oral cavity cancers were conflicting, and the investigators again did not find an increased risk of any sex-specific cancers.

The development of particular tumor types in scleroderma may in part depend on the severity and pattern of a given individual's end-organ involvement and/or the immunosuppressive medications they have received, although these associations have not been consistently characterized in the literature. These potential mechanisms linking cancer and scleroderma are discussed in more detail later.

Other demographic and phenotypic features of scleroderma that have been variably associated with an increased risk of cancer in early studies include older age of onset of scleroderma,[1,19–22] male sex,[6,8,9] smoking history,[23] and diffuse cutaneous involvement,[5] although these findings have not been consistently reproduced. Scleroderma autoantibody status, particularly anti-RNA polymerase III (anti-POLR3) positivity, has a dramatic effect on the overall risk and timing of cancer and may account for the discordant results from previous studies that did not control for this effect. This aspect of risk stratification is discussed in more detail elsewhere in this review.

POTENTIAL MECHANISMS LINKING CANCER AND SCLERODERMA

The relationship between cancer and scleroderma is likely complex and bidirectional. Cancers may emerge around the time of scleroderma onset or years after scleroderma diagnosis. These temporal relationships raise the question of whether malignancies or cancer treatments could trigger the development of scleroderma in some patients, whereas scleroderma or scleroderma therapies could increase the risk of subsequent cancer development in others. It is also possible that both diseases share a common inciting exposure or genetic predisposition.[24]

Data suggest that scleroderma disease activity and damage, particularly within individual organs, may predispose to malignant transformation within the same target tissues. For instance, patients with scleroderma may have a higher risk of esophageal cancer associated with severe reflux and Barrett esophagus, lung cancer in the context of known interstitial lung disease (ILD), liver cancer if there is overlap primary biliary cirrhosis, or thyroid cancer if there is autoimmune thyroiditis.[1,12,25,26] Data conflict as to whether scleroderma-ILD is a risk factor for lung cancer,[1,6,9,23,27] but the higher risk of lung cancers in patients with anti–topoisomerase 1 antibodies and reduced forced vital capacity is suggestive.[28] In a Japanese cohort of patients with scleroderma, risk factors for cancer were examined; all 10 lung cancer cases occurred

in patients with ILD.[4] Interestingly, of the 4 patients who had autopsies in this study, the primary lung cancer was found in tissue affected by ILD in all cases.

Another possibility is that cytotoxic therapies used to treat scleroderma could increase the risk of subsequent cancer. Cyclophosphamide is an alkylating agent that has been used to treat severe scleroderma cutaneous and pulmonary disease. Data from vasculitis, scleroderma, and lupus suggest that the risk of hematologic and bladder cancers may be increased with exposure to cyclophosphamide, in particular with higher cumulative doses and in smokers.[29–33] Increasingly, mycophenolate mofetil is used to treat active cutaneous disease, ILD, and myositis in scleroderma. The data on cancer risk with mycophenolate in the rheumatic diseases are less clear, as most of the studies are from the transplant area, where patients are often treated with combinations of immunosuppressive drugs. Data in the transplantation literature conflict as to whether there is a higher risk of lymphoproliferative diseases and nonmelanoma skin cancers,[34–37] with 1 recent report suggesting a higher risk of primary central nervous system lymphoma.[38] The data on cancer risk with immunosuppressive drugs in patients with scleroderma are limited. In our cohort, we have not observed an increased risk of cancer with immunosuppressive drug use, including cyclophosphamide and mycophenolate mofetil.[22] Whether these agents could directly promote malignant transformation is unclear. In the lupus literature, it has been postulated that immunosuppressive drugs may inhibit clearance of oncogenic viral infections, thereby increasing the risk of virus-associated cancers.[24,33] For discussion of other immunomodulatory agents commonly used in the rheumatic diseases and cancer risk, readers are referred to a recent review by Cappelli and colleagues.[39]

It is also important to note that patients with scleroderma may have a high cumulative exposure to ionizing radiation from medical tests over time, including plain radiographs, computed tomography (CT), and nuclear medicine studies.[40] This exposure could potentially increase the risk of cancer development.

A subset of patients develops scleroderma after cancer diagnosis and therapy. Cancer therapeutics, including chemotherapy, radiation therapy, and immunotherapy, may increase the risk of developing scleroderma. Case reports describe the development of scleroderma-like fibrosing syndromes and critical digital ischemia after exposure to bleomycin, gemcitabine, paclitaxel, and carboplatin.[41–46] Radiation therapy may trigger both cutaneous and pulmonary fibrosis; most reports describe localized scleroderma or exaggerated fibrosis developing in patients with known scleroderma.[1,47–49] It remains unclear whether de novo scleroderma could be a consequence of radiation exposure. A newer cancer therapeutic class, immune checkpoint inhibitors, works by blocking negative costimulatory receptors or ligands on T cells and antigen-presenting cells. These drugs can cause nonspecific T-cell activation and have resulted in several rheumatic immune-related adverse events. Recently, features resembling scleroderma have been reported after therapy with pembrolizumab or nivolumab (both PD-1 [programmed cell death protein 1] inhibitors).[50–53] Critical digital ischemia after immune checkpoint inhibitor therapy has also been reported.[54]

A close temporal relationship between the onset of cancer and scleroderma has been found in certain individuals, raising the question of whether scleroderma could be a paraneoplastic disease. This finding was initially observed in case reports and case series across a range of tumor types, although with particularly striking temporal clustering of breast cancer and scleroderma.[12,15–18] In 1 series, the breast cancer–scleroderma interval was 12 months or less in 27 of 44 individuals (61.4%), with simultaneous disease onset in 11 (25%).[17] Nearly half of this cohort was diagnosed with breast cancer before the onset of scleroderma. Further supporting the idea of

scleroderma as a paraneoplastic phenomenon are reports of cancer treatment resulting in dramatic improvements in scleroderma.[55,56] Although it has been challenging to discern whether this improvement is due to cancer treatment or simply the use of potent immunosuppression, a recent report of a patient improving solely with resection of tumor suggests that cancer itself may be a driver of scleroderma.[57]

UNIQUE AUTOANTIBODIES IDENTIFY PATIENT SUBGROUPS WITH A HIGH RISK OF CANCER-ASSOCIATED SCLERODERMA

Given data suggesting that scleroderma could be a paraneoplastic disease, our group hypothesized that tumor antigen expression might be associated with scleroderma-specific autoantibody responses. In an initial study of 23 individuals with both cancer and scleroderma, we found that those with anti-POLR3 antibodies had a significantly shorter cancer-scleroderma interval compared with those with anti–topoisomerase 1 or anticentromere antibodies (medians of −1.2 years, +13.4 years, and +11.1 years, respectively).[58] Furthermore, participants who had anti-POLR3 antibodies had robust nucleolar expression of RNA polymerase III in their cancerous cells, which was not found in cancer cells from the other antibody groups or in healthy control tissues.

This association between anti-POLR3 antibodies and increased risk of concurrent cancer and scleroderma onset has since been reproduced in multiple international cohorts, including from Australia, Italy, Japan, and the United Kingdom.[20,21,59,60] Recently, this finding was validated in the European League Against Rheumatism Scleroderma Trials and Research group (EUSTAR) cohort.[19] A total of 4986 individuals with scleroderma from 13 participating EUSTAR centers were included, and 158 participants with anti-POLR3 antibodies were compared with 199 anti-POLR3–negative controls matched for sex, cutaneous phenotype, age of scleroderma onset, and disease duration. Cancer was significantly more common in the anti-POLR3–positive group (17.7% vs 9.0%), particularly with respect to cancers diagnosed within 2 years of scleroderma onset (9.0% vs 2.5%). Individuals with a synchronous onset of cancer and scleroderma in the setting of anti-POLR3 antibodies were significantly older at scleroderma onset and more likely to have diffuse cutaneous disease. The risk of concurrent-onset nonbreast cancers and scleroderma was also significantly higher in men than in women. These demographic and phenotypic risk factors are consistent with the findings from early epidemiologic studies as discussed earlier.

The findings in our pilot study have also been validated using a much larger cohort of 1044 individuals from the Johns Hopkins Scleroderma Center cohort.[22] Logistic regression analyses were used to evaluate the relationship of overall cancer risk and a shortened cancer-scleroderma interval with autoantibody status, demographic features, and scleroderma phenotypic features. Once again, anti-POLR3 positivity was associated with a significantly increased risk of cancer diagnosis within 2 years of scleroderma onset (odds ratio, 5.08). There was also an increased temporal clustering of cancer and scleroderma in the group of participants who were negative for anticentromere, anti–topoisomerase I, and anti-POLR3 antibodies (CTP negative).

A major limitation of these prior studies was that cancer risk was investigated in patients with scleroderma with a given autoantibody compared with patients with scleroderma who were negative for that specificity. This study design does not permit determination of the magnitude or types of cancer at high risk compared with the general population, information that is needed to inform cancer screening strategies in scleroderma. To address this limitation, the authors examined cancer incidence within 3 years of scleroderma onset (ie, cancer-associated scleroderma) in distinct serologic and phenotypic groups and compared this with the US Surveillance, Epidemiology,

and End Results (SEER) cancer registry.[61] Of 2383 participants with scleroderma, 205 (~9%) had a history of cancer. Patients with anti-POLR3 antibodies and CTP-negative patients had a 2.8-fold and 1.8-fold increased risk of cancer within 3 years of scleroderma onset, respectively (**Fig. 1**). Within 3 years of scleroderma onset, patients with anti-POLR3 antibodies and diffuse cutaneous disease had a higher risk of breast cancer (SIR, 5.14), prostate cancer (SIR, 7.17), and tongue cancer (SIR, 43.9), whereas patients with anti-POLR3 antibodies and limited cutaneous disease had an increased risk of lung cancer (SIR, 10.4). Similarly, within 3 years of scleroderma onset, CTP-negative patients with limited scleroderma had a higher risk of

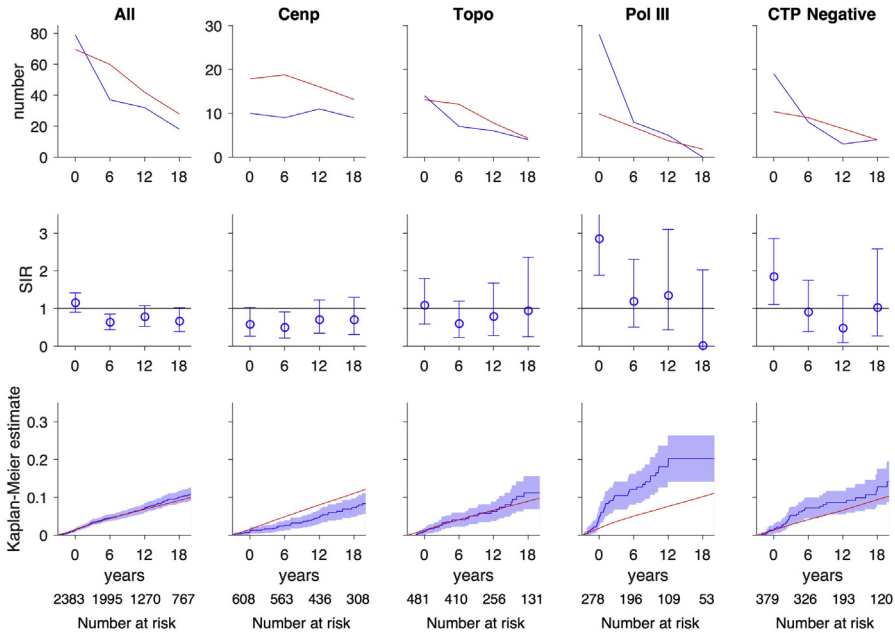

Fig. 1. Risk of all cancers over time. In each graph, the x-axis reflects time from scleroderma onset (defined as time zero). (*Top and middle rows*) Each time window represents a 6-year period (±3 years); for example, data plotted at time zero reflect cancer risk within plus or minus 3 years of scleroderma onset. The number at risk for each time window is denoted at the bottom of the graph. (*Top row*) The observed number of cancer cases (*blue*) is presented in comparison with the number of cancer cases that are expected based on SEER data (*red*). (*Middle row*) The ratio between the observed and expected cancer cases is presented as an SIR along with its 95% confidence interval. Values of 1 denote a cancer risk equivalent to that of the background population. (*Bottom row*) The cumulative incidence of cancer among patients with scleroderma (*solid blue line*) starting at 3 years before scleroderma onset is presented with 95% confidence intervals (*shaded blue region*). Red lines represent the expected cumulative incidence of cancer based on SEER data for the general population. Patients with scleroderma with anticentromere antibodies seem to have a decreased risk of cancer over time. Patients with scleroderma with anti-POLR3 antibodies and the CTP-negative group have an increased risk of cancer that is prominent at scleroderma onset. The cumulative incidence of cancer is significantly higher than that observed in the general population among patients with anti-POLR3 antibodies. Cenp, centromere; Topo, topoisomerase-1; Pol III, RNA polymerase III. (*From* Igusa T, Hummers LK, Visvanathan K, et al. Autoantibodies and scleroderma phenotype define subgroups at high-risk and low-risk for cancer. Ann Rheum Dis. 2018;77(8):1179-1186; with permission.)

breast cancer (SIR, 4.44) and melanoma (SIR, 7.10), and CTP-negative patients with diffuse scleroderma had an increased risk of tongue cancer (SIR, 40.5). When examining overall cancer risk, patients with anticentromere antibodies had a significantly lower risk of cancer than that expected in the general population (SIR, 0.59; see **Fig. 1**).

The CTP-negative subgroup in scleroderma is a heterogeneous population that likely consists of patients with many different scleroderma immune responses. It remains an important priority to identify the distinct subpopulations within CTP-negative patients, because this may guide risk stratification for cancer. Recently, our group has focused on autoantibody discovery in CTP-negative individuals in whom cancers were detected close to the time of scleroderma onset. In an initial investigation, phage immunoprecipitation sequencing was used for autoantibody discovery in participants who were either CTP negative with synchronous cancer and scleroderma, or had anti-POLR3 antibodies with or without cancer.[62] This method identified antibodies against the RNA binding region containing 3 (RNPC3), a component of the minor spliceosome complex, in 4 of 16 (25%) in the CTP-negative group and in none (0 of 32) in the anti-POLR3–positive group. These findings were subsequently reproduced in a larger population of 318 people with scleroderma and cancer.[63] Among them, a total of 12 (3.8%) had anti-RNPC3 antibodies. Compared with those with anticentromere antibodies, individuals with anti-RNPC3 or anti-POLR3 antibodies had a significantly higher risk of developing cancer within 2 years of scleroderma onset, with odds ratios of 4.3 and 4.5 respectively. Interestingly, 66.7% of the cancers in the anti-RNPC3 group were gynecologic tumors in women, with 50% having breast cancer, although this did not reach statistical significance across antibody subgroups because of small sample sizes.

The association between scleroderma-specific antibodies and cancer risk is likely limited to individuals who manifest clinical features of autoimmune disease and thus far does not seem to inform cancer risk in the general population. In a case control study of 50 women with breast cancer and 50 matched healthy controls (all without rheumatologic disease), all participants were negative for anti-POLR3 antibodies except for 1 control who was only borderline positive.[64] Similarly, anti-RNPC3 antibodies have not been detected in small comparison cohorts of healthy controls, patients with pancreatic cancer without rheumatic disease, and patients with lupus and cancer.[63]

EVIDENCE FOR A MODEL OF CANCER-INDUCED AUTOIMMUNITY

The striking co-occurrence of cancer and scleroderma onset in individuals with anti-POLR3 antibodies suggests a possible mechanistic link between the two disease processes and raised the question that cancer might be the trigger initiating autoimmunity in this subset of people. This possibility was investigated in a landmark study of tumors obtained from 16 patients with scleroderma, 8 of whom had anti-POLR3 antibodies, and 8 lacking these antibodies (they had antibodies against topoisomerase 1 or centromere, the two other prominent scleroderma antibody specificities).[65] In 6 of 8 (75%) cancers from the anti-POLR3–positive patients, alterations in the *POLR3A* gene locus were found. In contrast, none were detected in the tumors from the other 8 patients. Of the 6 patients with genetic abnormalities in *POLR3A*, 3 were somatic mutations; in each, this resulted in a single amino acid change (different in each patient). Furthermore, in 2 of these 3 patients, T cells that reacted with the mutated neoantigens were detected in peripheral blood. Given the rarity of POLR3A mutations in cancer, these findings are consistent with initiation of the anti-POLR3 immune

response by such somatic mutations. A second kind of genetic alteration was found in this study: 5 out of 8 patients had loss of heterozygosity (LOH) at the *POLR3A* gene locus. Because LOH was not detected in the cancers from the 8 patients lacking anti-POLR3 antibodies, it is likely that the anti-POLR3 antibody response participates in shaping cancer evolution.

Anti-POLR3 antibodies in the patients with somatic mutations cross-reacted with both the mutated and wild-type RNA polymerase III protein.[65] These data suggest a model of cancer-induced autoimmunity in scleroderma, where the anti-POLR3 immune response is initiated against the mutated protein in the cancer (ie, an anti-tumor immune response), followed by subsequent spreading to the wild-type protein (**Fig. 2**).[66] In susceptible hosts, this cross-reactive immune response could damage target tissue and become self-sustaining, resulting in scleroderma propagation.

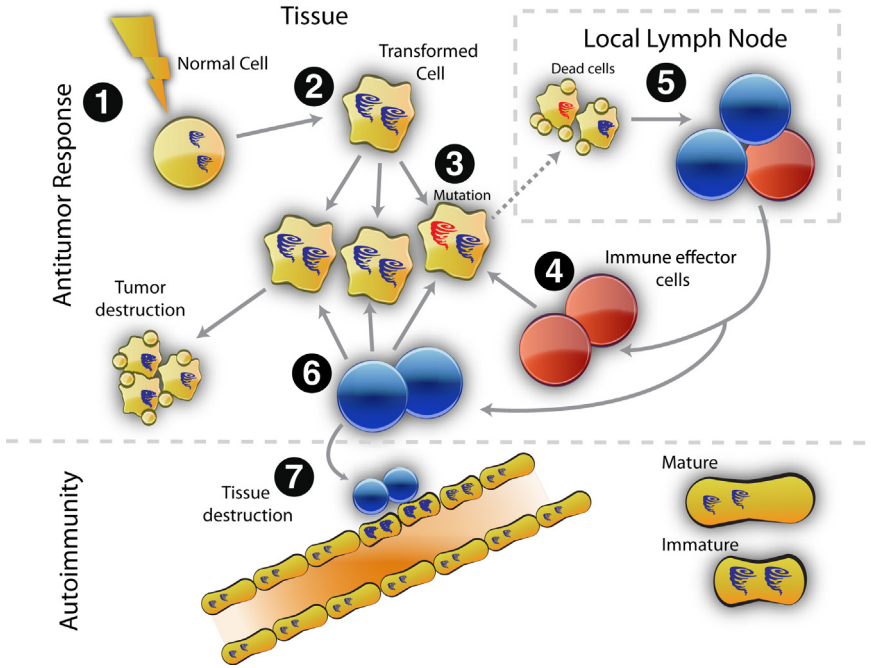

Fig. 2. Model of cancer-induced autoimmunity. Transformation of normal cells (1) may result in gene expression patterns that resemble immature cells involved in tissue healing (2). Occasionally, autoantigens become mutated (3); these are not driver mutations, and not all cancer cells have them. The first immune response is directed against the mutated form of the antigen (4), and may spread to the wild-type version (5). Immune effector cells directed against the mutant (*red*) delete exclusively cancer cells containing the mutation (6). Immune effector cells directed against the wild-type (*blue*) delete cancer cells without the mutation and also cross-react with the patient's own tissues (particularly immature cells expressing high levels of antigen, found in damaged/repairing tissue) (7). Once autoimmunity has been initiated, the disease is self-propagating. Immature cells (expressing high antigen levels) that repair the immune-mediated injury can themselves become the targets of the immune response, sustaining an ongoing cycle of damage/repair that provides the antigen source that fuels the autoimmune response. (*From* Shah AA, Casciola-Rosen L, Rosen A. Review: cancer-induced autoimmunity in the rheumatic diseases. Arthritis Rheumatol. 2015;67(2):317-326.; with permission.)

Additional studies are warranted to examine whether the mechanisms identified for RNA polymerase III apply more broadly to other subgroups with a high risk of cancer-associated scleroderma, such as patients with anti-RNPC3 antibodies.

CANCER PROTECTIVE IMMUNE RESPONSES MAY MODIFY CANCER RISK IN SCLERODERMA

Although the data suggesting a cancer-induced autoimmunity model in patients with scleroderma with anti-POLR3 antibodies are compelling, it is striking that 80% to 85% of these patients remain cancer free even over a prolonged period of follow-up. Could cancer be the initial trigger for scleroderma in patients with anti-POLR3 antibodies, with the subsequent antitumor response varying in its ability to eliminate the cancer or keep it in equilibrium without cancer emergence? Well-recognized features of the immune response include intramolecular and intermolecular spreading. That many scleroderma antibody specificities target multicomponent complexes, with multiple components being recognized by the antibody, is consistent with antigenic spreading. These features raised the question of whether targeting of additional autoantigens by the immune response could be cancer protective in anti-POLR3–positive patients with scleroderma.

To investigate this, our group identified 168 individuals with scleroderma and anti-POLR3 antibodies (based on clinically available assays and confirmed by enzyme-linked immunosorbent assay) with a roughly even mix of individuals with cancer or without cancer after at least 5 years of follow-up.[67] A comparison of the antibody profiles (generated by immunoprecipitation and visualized by fluorography) in these two subgroups showed clear enrichment of a 194-kDa protein targeted by antibodies in the cancer-negative group. This protein was subsequently identified as the catalytic subunit of RNA polymerase 1 (RPA194). When the full cohort was tested for antibodies against RPA194, anti-RPA194 was found to be significantly more common in the entire group without cancer (18.2%) compared with the group with cancer (3.8%), suggesting a potentially protective effect.

These findings raise the possibility that combinations of immune responses may have a previously unappreciated role in controlling cancer. They also highlight that knowledge of biomarkers that precisely define homogenous disease subgroups will enable improved precision in cancer prediction in relevant subsets. For instance, although patients with anti-POLR3 antibodies have a significantly increased risk of cancer-associated scleroderma that warrants intensive cancer detection strategies, patients with both anti-POLR3 and anti-RPA194 may not require additional cancer screening at scleroderma onset.

IMPLICATIONS FOR CANCER SCREENING

Given compelling data suggesting a model of cancer-induced autoimmunity in subsets of patients with scleroderma, important clinical questions arise. Do patients with new-onset scleroderma require intensive cancer detection strategies? If so, how do clinicians direct the right cancer screening tests to the appropriate patients, such that they maximize detection while minimizing the harms (ie, false-positive results and costs) of overscreening? If cancer is detected and treated early, could this effectively treat scleroderma and improve outcomes? Although there is not a strong evidence base to guide clinical decision making at this time, we share our current approach to cancer screening here.

Rheumatologists and primary care providers should ensure that all patients with scleroderma undergo comprehensive physical examination and age-based,

sex-based, and risk factor–based cancer screening tests according to recommendations for the general population.[68,69] Additional cancer screening studies may be considered based on the presence of scleroderma-specific risk factors. For example, patients with severe reflux that is refractory to standard proton pump inhibitor or H_2 blocker therapy should be referred for upper endoscopy to evaluate for Barrett esophagus, and serial endoscopies may be required if there is evidence of dysplasia or severe erosive esophagitis.[70] Patients with a persistent globus sensation or unexplained dysphagia may need otolaryngology evaluation given the increased risk of head and neck cancers in scleroderma.[61,71] If cirrhosis has developed, for instance because of primary biliary cirrhosis overlap, the American Association for the Study of Liver Diseases has recommended cross-sectional imaging with or without alpha fetoprotein assessment at intervals of 6 to 12 months.[72] Hematology referral may be warranted in patients with new, unexplained cytopenias. There may be a role for serial chest CT or low-dose chest CT monitoring for the development of lung cancer in patients with scleroderma with ILD, but this requires further study. Exposure to immunosuppressive therapies may also be an important risk factor. Patients with prior cyclophosphamide exposure may benefit from annual urinalysis and urine cytology, whereas patients treated with mycophenolate mofetil should be advised to report any new or changing skin lesions. If there is a history of extensive sun exposure or prior skin cancers, serial full skin examinations to evaluate for atypical lesions should be considered.

Although there are no published studies assessing cancer screening strategies in scleroderma, the data showing an increased risk of cancer around the time of scleroderma onset in distinct autoantibody subsets raises the question of whether aggressive cancer detection strategies should be considered. In dermatomyositis, another rheumatic disease where a mechanism of cancer-induced autoimmunity has been postulated, aggressive cancer screening measures, including CT of the chest, abdomen, and pelvis, and whole body PET-CT, are often performed clinically. Whether a similar approach in high-risk patients with scleroderma, such as those with anti-POLR3 antibodies or CTP-negative patients, would add value beyond traditional cancer screening tests requires further study. However, the data suggest that there may be a role for targeted cancer detection strategies based on autoantibody type and clinical phenotype.[61] For instance, anti-POLR3–positive patients with diffuse scleroderma have an increased risk of breast, prostate, and tongue cancer, suggesting a role for mammography, PSA assessment and prostate examination, and otolaryngology examination in these patients. Similarly, anti-POLR3–positive patients with limited scleroderma have an increased risk of lung cancer, suggesting a role for chest CT examination. Additional studies are underway to define the optimal approach to cancer screening in these high-risk subsets that maximizes cancer detection while minimizing the harms of overscreening.[73]

SUMMARY

The increased risk of cancer in scleroderma may be caused by multiple mechanisms, with biological data suggesting the development of cancer-induced autoimmunity in some patients. Recent epidemiologic studies indicate that autoantibody status and clinical phenotype may be useful filters to identify patient subgroups at high risk or low risk for cancer in scleroderma. Further work is needed to test the value of targeted cancer detection strategies in scleroderma, and to define whether early cancer detection and treatment improves scleroderma outcomes. It is also likely that careful investigation at the scleroderma-cancer interface may provide insight into mechanisms of

naturally occurring antitumor immunity and development of autoimmunity in the rheumatic diseases.

CLINICS CARE POINTS

- Scleroderma may be a paraneoplastic phenomenon in unique patient subgroups, including those with anti-RNA polymerase III antibodies or those who are negative for centromere, topoisomerase 1, or RNA polymerase III antibodies (CTP negative).
- All patients with new-onset scleroderma should undergo comprehensive physical examination and age-based, sex-based, and risk factor–based cancer screening tests.
- Recent data suggest that autoantibody and cutaneous subtype may define cancer risk, type, and timing in scleroderma. If validated, these findings may inform the development of targeted cancer screening guidelines.

DISCLOSURE

The authors have nothing to disclose.

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