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Cancer and Scleroderma: A Paraneoplastic Disease with Implications for Malignancy Screening

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Abstract

Purpose of review—Recent data suggest a paraneoplastic mechanism of scleroderma pathogenesis in unique subsets of scleroderma patients. In this article, we review these data, explore potential links between cancer and scleroderma, and propose an approach to malignancy screening in scleroderma.

Recent findings—Emerging data have demonstrated that patients with scleroderma and RNA polymerase III autoantibodies have a significantly increased risk of cancer within a few years of scleroderma onset. Genetic alterations in the gene encoding RNA polymerase III (*POLR3A*) have been identified, and patients with somatic mutations in *POLR3A* have evidence of mutation specific T cell immune responses with generation of cross-reactive RNA polymerase III autoantibodies. These data strongly suggest that scleroderma is a by-product of anti-tumor immune responses in some patients. Additional epidemiologic data demonstrate that patients developing scleroderma at older ages may also have a short cancer-scleroderma interval, suggestive of paraneoplastic disease.

Summary—Scleroderma may be a paraneoplastic disease in unique patient subsets. Aggressive malignancy screening in these patients may aid in early cancer detection. Further study is required to determine whether cancer therapy could improve scleroderma outcomes in this patient population.

Keywords

scleroderma; cancer; paraneoplastic

Introduction

As in many systemic inflammatory rheumatic conditions, patients with systemic sclerosis (scleroderma) have an elevated risk of cancer compared to the general population. This increased risk could be secondary to damage from scleroderma itself, cytotoxic therapies utilized to treat scleroderma, a common inciting exposure, or a genetic predisposition to the development of both cancer and autoimmunity. Cancer therapies may also trigger severe Raynaud's phenomenon or exaggerated fibrosis reminiscent of scleroderma. Importantly, a

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subset of patients develops cancer and scleroderma concurrently, suggesting that these two diseases are mechanistically associated. In this article, we will review the epidemiology of cancer in scleroderma and recent data supporting a paraneoplastic mechanism of scleroderma pathogenesis. Lastly, we will discuss implications these studies may have on the approach to screening scleroderma patients for an underlying malignancy.

Scleroderma patients have an elevated risk of many types of cancer

Many epidemiological studies have demonstrated that patients with scleroderma have an elevated age- and gender-adjusted risk of cancer compared to the general population (1-10). Since it is beyond the scope of this review to discuss all of these studies, we will focus on an excellent recently published meta-analysis of population-based cohort studies summarizing cancer risk in scleroderma (7). The authors pooled 6 original studies from Sweden, Scotland, Australia, US, Denmark and Taiwan with a total of 6641 scleroderma patients. Patients with scleroderma had an elevated risk of all cancers (pooled SIR 1.41, 95% CI 1.18, 1.68), and this risk was higher in men (pooled SIR 1.85, 95% CI 1.49, 2.31) than in women (pooled SIR 1.33, 95% CI 1.18, 1.49; $p < 0.01$ for comparison). Patients with scleroderma had an increased risk of lung (pooled SIR 3.18, 95% CI 2.09, 4.85), bladder (women only; pooled SIR 2.80, 95% CI 1.36, 5.76), hematologic (pooled SIR 2.57, 95% CI 1.79, 3.68), liver (pooled SIR 4.36, 95% CI 2.00, 9.51), and nonmelanoma skin (men only; pooled SIR 2.34, 95% CI 1.25, 4.59) cancers. While many studies have demonstrated a temporal clustering of scleroderma with breast cancer diagnosis (11, 12), the risk of breast cancer was not increased in scleroderma compared to the general population. Similarly there was not an increased risk of other gender-specific tumor types, such as prostate, cervical or uterine cancers. The authors also performed a secondary analysis of data from referral center studies and detected an increased risk of esophageal cancer (SIR 9.59, 95% CI 2.10, 43.88). Other studies have also demonstrated an increased risk of oropharyngeal cancers (5, 13), with one US study identifying a 25-fold increased incidence of tongue cancer (13).

It is important to define whether specific demographic or scleroderma phenotypic characteristics associate with an increased risk of cancer in scleroderma as these features may help identify patients who would benefit from targeted malignancy screening. While the data are controversial, some studies have suggested that the risk of cancer may be higher in patients with diffuse cutaneous disease (4). Similarly, interstitial lung disease may be a risk factor for lung cancer in scleroderma (1, 14, 15). Patients developing new onset scleroderma at an older age also have an elevated risk of cancer (see details below) (1, 16, 17).

Potential links between cancer and scleroderma

Patients with scleroderma may have an elevated risk of cancer due to disease activity or treatment related factors (18). Damage from chronic inflammation and fibrosis may lead to malignant transformation in certain organ systems. For example, ILD may be associated with lung cancer, and patients with severe, refractory gastroesophageal reflux disease and Barrett's esophagus may have a higher risk of esophageal cancers (19). An overlap syndrome with primary biliary cirrhosis may be seen in scleroderma, particularly among

patients with limited cutaneous disease and anti-centromere antibodies, and this may be associated with a higher risk of hepatic malignancies (20, 21). Immunosuppressive therapies used to treat scleroderma may also contribute to cancer risk. For example, mycophenolate mofetil and cyclophosphamide are often used to treat active diffuse cutaneous disease, ILD or myositis in scleroderma. It is well established that an increased cumulative dose exposure to cyclophosphamide raises the risk of bladder and hematologic malignancies (22, 23). Data on cancer risk with mycophenolate mofetil are primarily available from the organ transplant literature. To date, the findings are controversial, with some suggesting an increased risk of lymphomas and non-melanoma skin cancers (24-27). Complicating interpretation of the effect of mycophenolate use is the fact that these patients are often on combination immunosuppressive therapies.

While disease or scleroderma treatments may contribute to subsequent cancer risk, it is noteworthy that a subset of patients develops scleroderma after their cancer diagnosis. This raises the possibility that cancer therapies themselves may promote the development of scleroderma. Consistent with this hypothesis are case reports suggesting that bleomycin, carboplatin, gemcitabine, and paclitaxel may initiate severe Raynaud's phenomenon, critical digital ischemia, and/or skin fibrosis (28-33). Immunotherapies that eradicate tumors by harnessing host immune responses may trigger autoimmunity (34), and radiation therapy may stimulate development of localized scleroderma or exacerbate pre-existing scleroderma (although whether it could stimulate de novo scleroderma remains unknown) (35-37).

It is intriguing that scleroderma patients frequently have a striking family history of both malignancy and autoimmune diseases; whether this results from a shared genetic susceptibility or environmental exposure, such as silica that could initiate both diseases, awaits elucidation (38, 39).

Unique patient subsets have a temporal clustering of cancer with scleroderma onset

In some patients, cancer diagnosis and scleroderma onset are coincident temporally. This, together with reports of scleroderma improving with cancer therapy, raises the possibility that scleroderma is a paraneoplastic disease. In the Onishi meta-analysis, the risk of cancer was higher in the first 12 months after scleroderma diagnosis (pooled SIR 2.79, 95% CI 1.81, 4.31) than >12 months after scleroderma diagnosis (pooled SIR 1.40, 95% CI 1.22, 1.61; $p=0.003$ for comparison) (7). Consistent with this, we determined that many (22.7%) cancer diagnoses occurred within 2 years of the first non-Raynaud's scleroderma symptom in a recent study of the Johns Hopkins Scleroderma Center cohort (Figure 1) (17). While there could be a cancer detection bias in patients with new onset disease, many cancer cases were also diagnosed shortly before the first clinical signs of scleroderma were appreciated.

In an initial pilot study of 23 scleroderma patients with cancer, we demonstrated that patients with RNA polymerase III autoantibodies have a striking temporal clustering of cancer diagnosis with the first clinical signs of scleroderma (40*). Furthermore these patients had unique nucleolar expression of RNA polymerase III in their cancerous cells that was not detected in patients with other scleroderma autoantibodies or in normal control

tissues (40). These data suggested that scleroderma autoantigen expression in cancer cells associated with scleroderma-specific immune responses.

The increased risk of concurrent cancer with scleroderma onset among patients with RNA polymerase III antibodies has now been confirmed in 4 other studies (16, 17, 41, 42). In an Australian study of 451 scleroderma patients, those with anti-RNA polymerase III antibodies had a 4.2 fold increased odds of cancer within 5 years of scleroderma onset (95% CI 1.3, 13.4) (16). In another investigation of 2177 scleroderma patients in the Royal Free Hospital scleroderma cohort, patients with cancer within 3 years of scleroderma onset were much more likely to be anti-RNA polymerase III antibody positive (55.3%) than anti-topoisomerase 1 (6.3%, $p < 0.0001$) or anticentromere (6.8%, $p < 0.001$) positive patients (42). In our US cohort, we studied 1044 scleroderma patients (17). Those with RNA polymerase III autoantibodies had a 5.08 fold increased risk of cancer within 2 years of scleroderma onset (95% CI 1.60, 16.1) (17). An older age of scleroderma onset also strongly associated with a clustering of cancer with scleroderma (17). These data suggest that patients with new onset scleroderma and RNA polymerase III autoantibodies, or an older age of scleroderma onset, may benefit from aggressive malignancy screening at diagnosis.

All of these cohorts also had scleroderma patients with contemporaneous cancer and scleroderma onset in other autoantibody groups. For patients with anti-topoisomerase 1 antibodies and those who were ANA positive but negative for centromere, topoisomerase 1 and RNA polymerase III autoantibodies, the clustering of cancer diagnosis with scleroderma onset was most remarkable among patients developing scleroderma at older ages (Figure 2) (17). There are several possible explanations for the shortening of the cancer-scleroderma interval among older patients developing scleroderma. Patients with a young age of scleroderma onset may develop later cancers due to damage from the disease or therapies used to treat it, whereas patients with an older age of scleroderma onset may have paraneoplastic disease (see below) (17). Alternatively, patients with a young age of scleroderma onset may be able to mount robust anti-tumor immune responses that hold subclinical malignancies in equilibrium for years until the cancer mutates and evades the anti-tumor immune response, thereby resulting in a long cancer-scleroderma interval; in contrast, older patients developing scleroderma may have poorer quality immunosurveillance of malignancies resulting in concurrent emergence of cancer and scleroderma (17). The data demonstrating a clustering of cancer with scleroderma onset in other autoantibody groups is intriguing and raises the question of whether cancer may be a trigger of autoimmunity more broadly among patients with scleroderma (43).

Biologic data suggesting a paraneoplastic model of scleroderma pathogenesis

Our earlier observation in scleroderma patients with anti-RNA polymerase III autoantibodies (40) of a close temporal relationship between the clinical onset of scleroderma and cancer diagnosis suggested that the two processes may be mechanistically linked. To address whether alterations in the gene encoding RNA polymerase III (ie, the *POLR3A* gene locus) in tumors may trigger autoimmunity, we studied tumors from 8 anti-RNA polymerase III antibody-positive scleroderma patients, and from another 8

scleroderma patients with antibodies against either topoisomerase I or centromere proteins (44). In 6/8 (75%) of the anti-centromere positive patients, the *POLR3A* locus was genetically altered. In contrast, no such alterations were found in tumors from the other group of scleroderma patients. 3/6 (50%) of the genetic alterations we found were somatic mutations in *POLR3A*, with the mutation in each causing a single amino acid change (of note, the mutations were different in each patient). Since mutations in *POLR3A* are rare in cancer, this study suggests that mutated RNA polymerase III proteins are immunogens that initiate the anti-RNA polymerase III antibody response. Interestingly, there was loss of heterozygosity in 5/8 (62.5%) of the anti-RNA polymerase antibody positive patients. Since this was not noted in cancers of the scleroderma patients with other antibody specificities, this finding is compelling evidence that the immune response against RNA polymerase III may shape how cancers evolve (43, 44).

It is noteworthy that antibodies from all the patients with *POLR3A* mutations recognized the wild type (WT) and mutated protein equally (44). This is consistent with evidence from Lin et al (45) that modified self-antigens can initiate T cell immune responses to altered antigens, producing B cell responses that recognize the WT and modified proteins equally. Building on this concept, we have proposed the following model of cancer-induced scleroderma (Figure 3) (43). Gene expression patterns similar to those of immature cells involved in tissue healing may result when normal cells become transformed. During this process, mutations in RNA polymerase III proteins may occasionally be generated. When these occur, they are found in some, but not all, of the cancer cells since they are not driver mutations. A mutant-specific T-cell response is initiated, which subsequently spreads to the WT protein. While immune effector cells directed against mutant RNA polymerase III delete only those cancer cells with the mutation, those directed against the WT form delete cancer cells without the mutation. In addition, the latter cross-react with self-tissue, thus initiating scleroderma. Autoimmunity subsequently becomes self-propagating, likely because immature cells expressing robust amounts of targeted antigens are themselves targeted by the immune response.

That the majority (~80%) of anti-RNA polymerase III antibody-positive scleroderma patients do not have an associated malignancy is informative (17, 43). This indicates that an anti-tumor immune response may eradicate an occult malignancy in most of the scleroderma patients in this disease group. In those anti-RNA polymerase III antibody positive patients in whom a malignancy does emerge, reasons for the temporal relationship between detection of both these diseases is discussed above.

In our original description of the short cancer-scleroderma interval in patients with RNA polymerase III antibodies, we noted a second group of scleroderma patients with a similar temporal clustering (40). These patients were negative for the most commonly known scleroderma antibody specificities (that is, ANA positive but having no antibodies against topoisomerase I, centromere proteins and RNA polymerase III). The data presented in Figure 2 of this review (depicted as the “Other group”, and discussed above; see also reference (17)) confirms our earlier observation in this regard. Together, these data indicate that other autoantigens of relevance to understanding the interface between scleroderma and cancer wait to be defined (43).

Implications for cancer screening and scleroderma therapeutics

These data strongly suggest that a subset of patients with scleroderma have cancer-induced autoimmunity, raising the question of whether early cancer diagnosis and treatment could induce remission of scleroderma. Further studies are required to identify the optimal cancer screening algorithm that should be performed in patients with new onset scleroderma. A potential framework to guide cancer screening is proposed in Figure 4. It is our standard practice to recommend age- and gender-appropriate cancer screening in scleroderma patients. This includes a comprehensive physical examination including palpating anterior and posterior cervical, supraclavicular, axillary and inguinal lymph nodes; scanning the skin for atypical lesions, particularly those with asymmetry, indistinct borders, color variegation, or large diameter (> 6 mm); careful visualization of the oral cavity; and palpating for thyroid nodules. For older patients developing new scleroderma, we would suggest updating a colonoscopy or Pap smear once even if the patient has passed the typical age for colon cancer (>75) or Pap smear (>65) screening. Currently in the US, it remains controversial as to when and how often women should undergo mammographic screening for breast cancer. Because of the close temporal relationship between breast cancer and scleroderma onset, we recommend initiating annual mammography starting at 40 years of age. Further targeted screening may be required based on the presence of specific risk factors as delineated in Figure 4. Lastly, a subset of patients may benefit from aggressive cancer screening due to concern for paraneoplastic disease. We have denoted these patients as having a “red flag” such as RNA polymerase III autoantibodies, an older age of scleroderma onset, atypical or treatment unresponsive disease, profound constitutional symptoms or weight loss, or a striking personal or family history of cancer. More extensive imaging, such as a CT of chest, abdomen and pelvis or whole body PET scan, and laboratory testing (serum/urine protein electrophoresis, peripheral blood flow cytometry and tumor markers) may be warranted in these patients.

Conclusion

Recent data strongly suggest that scleroderma may be a paraneoplastic disease in some patients. These emerging findings raise the intriguing possibility that cancer therapy might be effective at treating scleroderma. While the cancer-scleroderma relationship is most striking in patients with RNA polymerase III autoantibodies, the mechanisms and principles identified thus far likely apply to other patients with scleroderma, and more broadly across the spectrum of autoimmune rheumatic diseases. Further investigation is warranted to identify other relevant autoantigens that associate with paraneoplastic disease, particularly among patients developing scleroderma at an older age, as this may help define the population of patients who would benefit from enhanced cancer screening.

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diagnosis with scleroderma onset among patients with RNA polymerase III autoantibodies. Patients with scleroderma and RNA polymerase III autoantibodies had unique nucleolar expression of RNA polymerase III in their cancerous tissues, suggesting that autoantigen expression in tumors associates with scleroderma specific immune responses. [PubMed: 20506513]

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Key Points

- There is a close temporal relationship between cancer diagnosis and scleroderma onset in a subset of patients, suggesting that these two diseases may be mechanistically linked.
- Patients with RNA polymerase III autoantibodies or an older age of scleroderma onset have a higher risk of cancer-associated scleroderma.
- Enhanced cancer surveillance and screening may be warranted in patients at risk of cancer-associated scleroderma, as early cancer detection and therapy may improve scleroderma outcomes.

Figure 1. Examination of the cancer-scleroderma interval (years) in the Johns Hopkins Scleroderma Center cohort (17)

Negative values: cancer diagnosis preceded the first clinical signs of scleroderma. Positive values: cancer diagnosis followed scleroderma onset.

Figure 2. Relationship between age of cancer diagnosis and age at scleroderma onset by autoantibody status (17)

Panel A: The red line identifies where there is perfect concordance between cancer diagnosis and scleroderma onset, i.e. the cancer-scleroderma interval is zero. Panel B: The distributions of age at scleroderma onset and age at cancer diagnosis are illustrated using a kernel density function. Patients with RNA polymerase III antibodies and cancer almost unvaryingly have a close cancer-scleroderma interval, whereas patients with anti-centromere antibodies infrequently have a close cancer-scleroderma interval. Among patients with topoisomerase 1 antibodies and those who are ANA positive but negative for RNA polymerase III, topoisomerase 1 and centromere antibodies (the Other group), the cancer-scleroderma interval narrows with older age at scleroderma onset.

Figure 3. Paraneoplastic model (43)

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 (depicted in red) delete exclusively cancer cells containing the mutation (6). Immune effector cells directed against the wild type (depicted in 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.

Figure 4. Proposed cancer screening algorithm in patients with new onset Scleroderma
Comprehensive physical examination and age- and gender-appropriate cancer screening are suggested for all patients. Further targeted testing is recommended for patients with specific risk factors (46-49). Aggressive cancer screening may be warranted for patients who have “red flags,” such as RNA polymerase III autoantibodies or an older age of scleroderma onset.