LEAP ROUNDS

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School of Medicine
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At the Interface of Scleroderma and Cancer

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Target Cancer Screening

SCLERODERMA AND CANCER

INTERVIEW: AMI SHAH, M.D., M.H.S.

In 2015, Johns Hopkins scientists proved that scleroderma is often a casualty of war: it is the unfortunate consequence of the body's battle to fight off cancer. We have since learned much more about the complex, bidirectional relationship between cancer and autoimmunity. It is a tale told by antibodies: a paraneoplastic disease, in which naturally occurring anti-tumor immune responses lead to autoimmunity.

How can we use this knowledge to take better care of our patients? Specifically, what are the clinical implications for cancer screening in patients at high risk for cancer-induced scleroderma?

SCLERODERMA:

50	63	37
active research protocols	percent limited subtype	percent diffuse subtype

Antibodies Predict Phenotype

Scleroderma is an incredibly heterogeneous disease that consists of several distinct sub-phenotypes. The simple construct of limited vs. diffuse does not fully explain a patient's likely trajectory or disease course; for example, patients with diffuse scleroderma can have significant vascular disease, while those with limited scleroderma can still develop interstitial lung disease. At the Johns Hopkins Scleroderma Center (JHSC), we commonly study scleroderma-specific autoantibodies as biomarkers, because we know that these associate with very distinctive clinical phenotypes.

The Patient Who Ignited the Spark

Our interest in studying these biomarkers began in 2007 with one remarkable patient: a 43-year-old woman who came to our clinic. She had features of scleroderma before being diagnosed with small-cell lung cancer. She was treated with chemotherapy, radiation therapy, and prophylactic brain irradiation, and within a year, her Raynaud's worsened, her hands became more swollen, and she developed rapid, diffuse skin thickening involving her entire body. The thickening was clearly worse in the radiation field but extended well beyond it. When she was seen in our center, her autoantibody labs showed that she was positive for anti-RNA polymerase III (anti-RNA pol3).

Why were these two diseases occurring together in time? Does this simply reflect the increased risk of lung cancer that exists in patients with scleroderma? Or could scleroderma actually be a byproduct of an anti-tumor immune response? And, could distinct autoantibodies somehow provide insight into a process that's occurring at disease initiation? Could they be fingerprints?

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In a subsequent study, we recruited 23 scleroderma patients with cancer and examined their cancerous tissue specimens. We were specifically interested in this issue of timing: how long had the patients had scleroderma when they were diagnosed with cancer? We looked at the distribution of this interval between cancer and scleroderma across different autoantibody subgroups. We had patients who were positive for anti-RNA pol3, anti-topoisomerase 1 (anti-Scl-70), anti-centromere antibodies (ACAs), and a group of patients negative for these three tested autoantibodies.

We were very surprised to find that patients with anti-RNA pol3 antibodies had a very tight clustering between cancer and the first clinical signs of scleroderma, with cancer shortly preceding scleroderma onset. This pattern was very different from that of the patients with anti-Scl-70 or ACAs. Indeed, when we looked back at our much larger JHSC cohort, we confirmed that scleroderma patients with anti-RNA pol3 antibodies had a more than fivefold increased risk of cancer within two years of scleroderma onset, compared to scleroderma patients who were negative for these autoantibodies. These findings have now been independently confirmed in multiple international scleroderma cohorts.

Next, in collaboration with scientists Bert Vogelstein and Ken Kinzler, we studied 16 scleroderma patients with cancer and performed genetic sequencing of their tumor cells. Eight of these patients were positive for anti-RNA pol3, and 8 were positive for anti-Scl-70 or ACA antibodies. Here again, the patients with anti-RNA pol3 had a very short interval between cancer and the first clinical signs of scleroderma, often with cancer shortly preceding scleroderma onset. Of these patients, three had evidence of somatic mutations at the POLR3A locus in their cancerous tissue, which was not seen in the other antibody subgroups. Five anti-RNA pol3 patients had evidence that they had lost the piece of DNA encoding POLR3 from one of their chromosomes (called loss of heterozygosity). In total, 75 percent of patients with anti-RNA pol3 had genetic abnormalities at the locus encoding that protein. This is not a feature of any patients with other antibodies and is very uncommon in cancers

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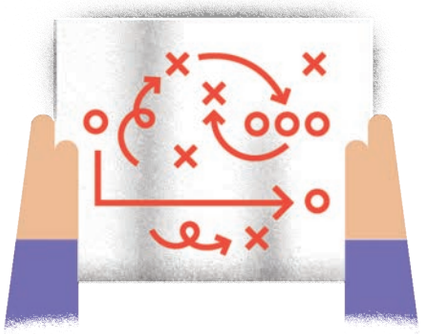
Dr. Shah's clinical practice encompasses the broad spectrum of patients with scleroderma, Raynaud's phenomenon and related fibrosing syndromes. Her clinical research program focuses on the interface between cancer and autoimmunity in scleroderma, myositis and the newly emerging area of rheumatic immune-related adverse events due to immune checkpoint inhibitor therapy. Dr. Shah also has an active research program in other clinical and therapeutic aspects of scleroderma, including early detection of cardiopulmonary complications and improving outcome measures and therapeutics for Raynaud's phenomenon. In 2018, Dr. Shah's research contributions were recognized at the 5th Systemic Sclerosis World Congress with the Edith Busch Prize for Young Investigators. In 2020, she was honored to receive the Henry Kunkel Young Investigator Award from the American College of Rheumatology.

from patients without scleroderma. Immunological studies showed that the immune response recognized the mutated and wild type versions of the protein.

These data suggested that patients who acquire a mutation in an autoantigen in their cancer may develop an immune response that's initially specific to the cancer. If this immune response spreads to the unmutated autoantigen, this can be beneficial and result in additional anti-cancer effect. But this could also lay the groundwork for the development of autoimmunity. Patients with anti-RNA pol3 have a high risk of cancer at the time of scleroderma onset. When you look in our JHSC cohort, about 20 percent of these patients with anti-RNA pol3 have a cancer detected, and 80 percent of these patients do not.



There may be a way to target screening strategies based on distinct autoantibody subsets and clinical phenotypes.

Are there other features that can differentiate a group of patients who have a cancer vs. those who do not?

There are really not clinical characteristics that differentiate these groups of patients. But the breadth and strength of the immune response may provide insight into those who have evidence of a malignancy vs. those who do not. For example, we can see that anti-RNA pol3-positive patients *with cancer* have a much higher titer immune response than scleroderma patients with the same autoantibody *who do not have cancer*.

Are there other differences in the immune response in those with vs. without cancer? Scientist Livia Casciola-Rosen has discovered that indeed, scleroderma patients with anti-RNA pol3 who do not have cancer are much more likely to have an additional autoantibody to the large subunit of RNA polymerase 1. These data suggest to us that an immune response that's targeting both the pol1/3 machinery may actually confer protection from cancer.

Now we get to the really big questions that could be practice-transformative:

- If cancer could be a trigger for scleroderma in distinct immune response subsets, who should we screen for cancer, and when should we perform screening tests?
- What tumor types should we be looking for?
- If cancer and scleroderma co-exist, how do we treat in that scenario — and could cancer therapy be effective scleroderma therapy?

With scientist Takeru Igusa, we compared cancer incidence in our JHSC cohort to the general population using the US Surveillance, Epidemiology, and End Results (SEER) Program cancer registry data. Among other findings: In patients with anti-RNA pol3 who have *diffuse* scleroderma, there is an increased risk of breast, prostate, and tongue cancer, whereas among anti-RNA pol3-positive patients with *limited* scleroderma, there is an increased risk of lung cancer.

These data suggest that there may be a way to target screening strategies based on distinct autoantibody subsets and clinical phenotypes. For patients with anti-topo antibodies, the risk of cancer is equivalent to what you would expect in the general population. But much to our surprise, patients with ACA actually have far fewer cancer cases observed than expected, and a lower cumulative incidence of cancer over time.

Conclusions

There is a close temporal relationship between cancer and scleroderma onset among patients with anti-RNA pol3. We believe there's compelling biologic data that suggests cancer-induced autoimmunity in these patients. We've also found some evidence to suggest that certain immune responses or combinations of immune responses (POL1 plus POL3) may associate with a lower incidence of cancer and could actually be cancer-protective. ACA is associated with a striking decrease in cancer risk. We believe that autoantibody and phenotype can define cancer risk and type in scleroderma, and we are working to validate these findings in an external patient cohort. We are now testing cancer detection strategies (novel liquid biopsy techniques) and imaging measures (breast MRI and PET/CT) in high-risk subgroups.

FURTHER READING

Close temporal relationship between onset of cancer and scleroderma in patients with RNA polymerase I/III antibodies.
Arthritis Rheum
2010, PMID:20506513

Association of the autoimmune disease scleroderma with an immunologic response to cancer.
Science
2014, PMID:24310608

Examination of autoantibody status and clinical features associated with cancer risk and cancer-associated scleroderma.
Arthritis Rheumatol
2015, PMID:25605296

Autoantibodies and scleroderma phenotype define subgroups at high-risk and low-risk for cancer.
Ann Rheum Dis
2018, PMID:29678941

Protective effect against cancer of antibodies to the large subunits of both RNA polymerases I and III in scleroderma.
Arthritis Rheumatol
2019, PMID:30888702

705 PATIENTS

with at least one cancer at the Johns Hopkins Scleroderma Center

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Patients in the Johns Hopkins Scleroderma Center's research cohort

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PATIENTS: 443 997 1552

PHYSICIANS: 410 550 7715