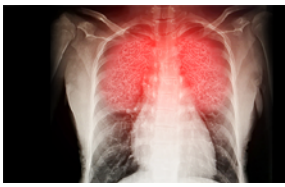

SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE:
MAKING CONNECTIONS, ELEVATING CARE

OVERVIEW

Renowned pulmonologist, Imre Noth, MD, and scleroderma expert rheumatologist, Elizabeth Volkmann, MD, MS, discuss the importance of screening patients with systemic sclerosis (SSc) to identify those at risk for interstitial lung disease (ILD) even before respiratory symptoms are reported. Risk factors, burden of disease, and comorbidities associated with SSc-ILD are presented. This rare multisystemic disease affects the lungs, heart, and kidneys, in addition to the skin and gastrointestinal tract. Careful monitoring and ongoing evaluation are required to minimize lung complications. The latest first-line treatments and combination strategies are reviewed, along with data of FDA-approved targeted therapies as the faculty provide insights to individualize treatment so as to improve patient outcomes. Faculty case presentations describe treatment strategies and address how best to optimize clinician-patient communication in this innovative education format.

CONTENT AREAS:

- Epidemiology and burden of disease
- Screening
- Multisystemic disease
- Associated comorbidities
- Treatment options and therapeutic strategies
- Case studies: Clinician-patient communication and treatment plan

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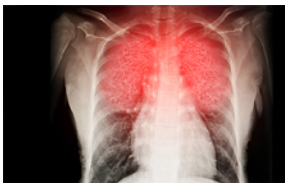
CME INFORMATION

Target Audience

This activity was developed for pulmonologists, radiologists, rheumatologists, dermatologists, and primary care physicians, as well as other clinicians who care for patients with interstitial lung disease.



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Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Recognize the healthcare and economic burden associated with systemic sclerosis (SSc)-associated interstitial lung disease (ILD) and the need to evaluate, monitor, and manage lung involvement in patients with SSc
- Identify patients with SSc to screen for ILD
- Select appropriate treatment for patients with SSc-ILD
- Identify the risk factors for SSc-ILD and its associated comorbidities, and recognize the need to manage comorbidities in patients with SSc-ILD
- Apply strategies for optimal clinician-patient communication and for education of patients with SSc-ILD

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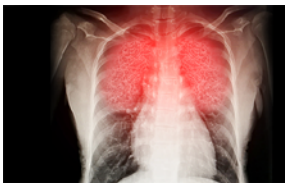

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The estimated time to complete the activity is 2.0 hours.

This activity was released on February 28, 2022 and is eligible for credit through February 28, 2023.

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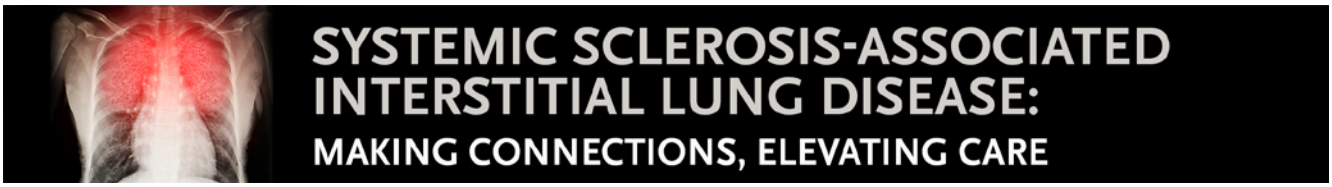
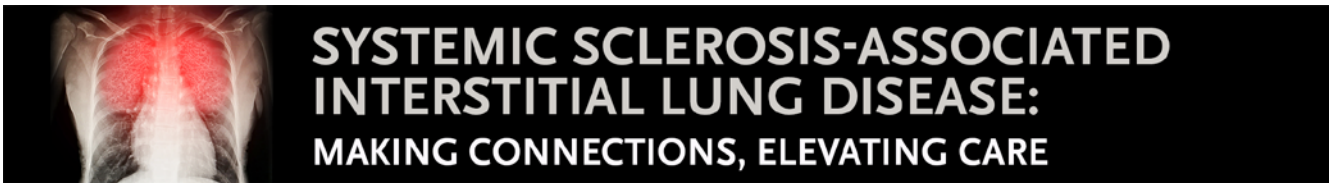


Abbreviations

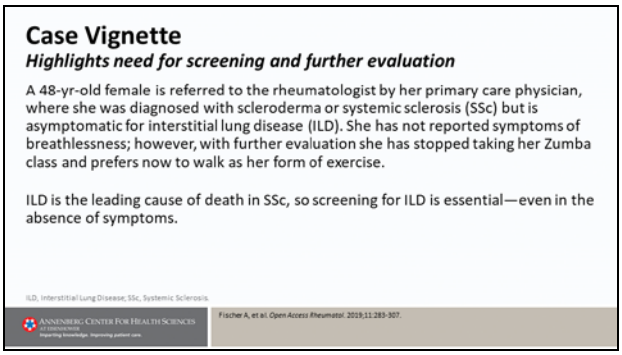
ACR, American College of Rheumatology
CCL18, CC chemokine ligand 18
CK, creatine kinase
CT, computed tomography
CTD-ILD, connective tissue disease-associated interstitial lung disease
CRP, C-reactive protein
DLCO, diffusing capacity of the lungs for carbon monoxide
esr, erythrocyte sedimentation rate
EULAR, European Alliance of Associations for Rheumatology
FEV1, forced expiratory volume over 1 second
FVC, forced vital capacity
HRCT, high-resolution computed tomography
HP, hypersensitivity pneumonitis
HPAF, hypersensitivity pneumonitis with autoimmune features
ILD, interstitial lung disease
IPAF, interstitial pneumonia with autoimmune features
ipf, idiopathic pulmonary fibrosis
KL-6, Krebs von den Lungen-6
mRSS, modified Rodnan skin score
NSIP, nonspecific interstitial pneumonia pattern
PE, pulmonary embolism
PFT, pulmonary function test
PM-Scl, anti-polymyositis-Scl
Scl, scleroderma
SF-36, Short Form 36 health survey questionnaire
SGRQ, St. George's Respiratory Questionnaire
TDI, Transitional Dyspnea Index
TTE, transthoracic echocardiogram
UIP, usual interstitial pneumonia
VATS, video-assisted thoracoscopic surgery



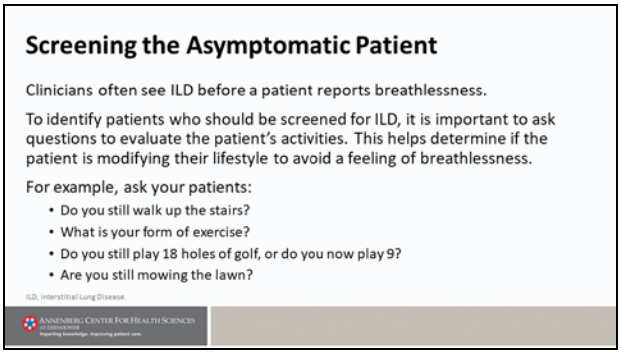
Editor's Note: This is a transcript of a webcast presented in January 2022. It has been edited and condensed for clarity.

PREVALENCE, PATIENT BURDEN, AND THE NEED FOR SCREENING SSC PATIENTS FOR ILD

Dr. Noth: We're going to start with our red line module, which is going to discuss the prevalence, patient burden, and need for screening of scleroderma patients for interstitial lung disease. I want to start with a case vignette that highlights the need for screening and further evaluation.



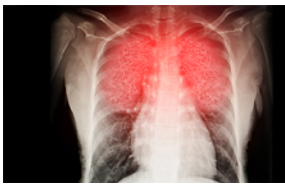
This is a 48-year-old woman who was referred to the rheumatologist by her primary care physician when she was diagnosed with the scleroderma—also referred to as systemic sclerosis—and was asymptomatic for an underlying interstitial lung disease. She has not reported any symptoms of breathlessness; however, with further evaluation, she has stopped taking her Zumba class and prefers now to walk as her form of exercise, suggesting that she might be experiencing some level of deficit. ILD is the leading cause of death in scleroderma,[1] and so screening for ILD is really very essential, even in the absence of symptoms.



As clinicians, we often see ILD in patients before they report that breathlessness, and so we want to be looking for and screening patients for interstitial lung disease with some basic questions in regard to their lifestyle, so we can pick up on deficits before they may have an appreciation of it. Do you still walk up the stairs? What's your exercise performance like? I often use the golf analogy with many because 18 holes of golf becomes 9, and 9 holes of golf becomes a golf cart. They quit carrying their clubs, and they quit walking on their own, and really, they end up leaning on crutches, assuming that it might be age-related or reconditioning or some other process. And they might ask someone to start mowing their lawn. So, it's just a way of getting at it.

EPIDEMIOLOGY OF SSC

Dr. Noth: When we think about the epidemiology, we have to understand that overall scleroderma is really a rare connective tissue disorder on the whole, but it's very important because it affects multiple organ systems.[2] The interstitial lung disease component is incredibly common in scleroderma, with up towards of 30%-40% presenting with some level of significant interstitial lung disease, and it carries a mortality as high as 40% over a 10-year period.[2] The onset tends to be within the first 5 years of the first non-Raynaud's phenomenon as a presentation within scleroderma. And the interstitial abnormalities



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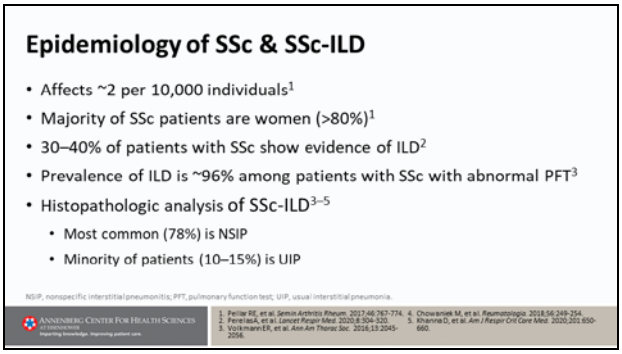
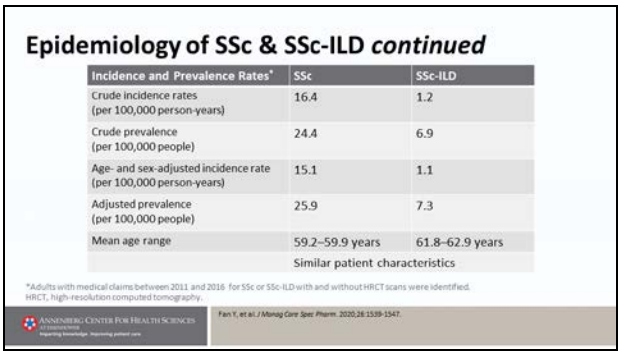
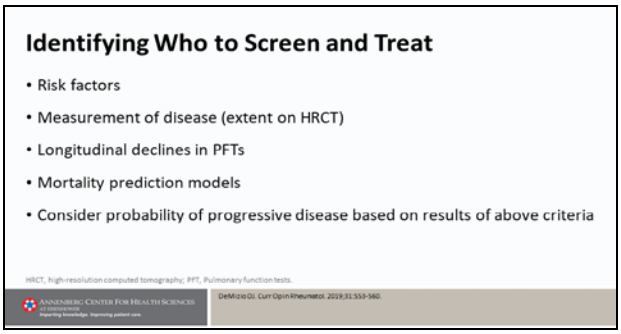
become evident on a CT scan almost immediately, with upwards of 80% experiencing findings on a CT scan, making it probably our strongest tool for picking up subclinical disease. Because it's so prevalent and the rate, of course, of clinical disease is much lower than what we're picking up on the CT scan, the subclinical level is quite high in patients on the whole.



We know that it's affecting about 2 per 10,000 individuals, and that the majority are women—greater than 80%.[1] We know that the prevalence of ILD is greater than 96% of those with an abnormal PFT [pulmonary function test].[1] So, you've got to flip your thinking around that. What I'm saying is if we see a lung deficit on the pulmonary function test, well then if we get the CT scan, we're going to spot it in 96% of the cases. It's going to be there. And when we look at the underlying histopathology, the most common presenting pathology is a nonspecific interstitial pneumonia pattern. I always joke that's a terrible name. It's actually reasonably specific; it's just that it wasn't attributed to any specific underlying disease entity, and it seems to present in 75%-80% of the cases where we find scleroderma. A minority of 10 to 15 seem to have a usual interstitial pneumonia pattern and, of course, that pattern is more ominous.[1,2]



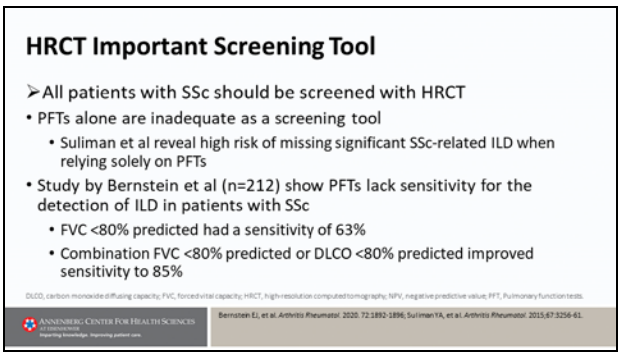
When we think about the epidemiology of scleroderma and scleroderma-associated interstitial lung disease, we can look at the incidence and prevalence rates. Per 100,000 person years, you clearly see a separation where the interstitial lung disease is going to be much lower than the scleroderma lung group as a whole. But what really becomes informative is the prevalence-to-incidence rate, which is only at 1.5 on this table for scleroderma proper, but it's nearly six-fold on the interstitial lung disease,[1] really suggesting that, of course, this is screening-dependent. We need to be looking for it in order to find it, because we know what the rate is overall. And we certainly can age-and-sex adjust for the incidence rate based on gender, and you can see those differences being applied, as well. And then finally, when we take a look at the adjusted prevalence, we can see that is going to feed back out, and we get a median age range, which is really pretty equivalent between basic scleroderma and scleroderma with an underlying interstitial lung disease of roughly 60 years of age.



Well, as we start to talk about identifying who to screen and who to treat, I'd like to bring Elizabeth in to discuss a little bit about what she's thinking about when she sees them in her clinic, because, from my perspective, of course, I'm focused on that CT scan and those pulmonary function tests as a means of really gauging whether or not there's clinically meaningful disease and the level of that disease on the CT scan as a screening tool.

Dr. Volkmann: That's a great question, and I think historically what we did as rheumatologists is we would rely on symptom assessment or PFT screening to decide whether to order a CT scan on a patient. So, if a patient reported shortness of breath or cough, or they had a restriction on PFTs, that would then prompt ordering a CT scan. But I think we've evolved from that practice pattern to now ordering a CT scan on all patients, and the reason being—and I'd love to hear your thoughts on this—is that many patients, early in the course of their interstitial lung disease, can be asymptomatic or they may be making those lifestyle adjustments that you talked about to avoid feeling breathlessness. In addition, they can have normal pulmonary function tests. You know, maybe their FVC [forced vital capacity] a couple of years ago was 110% predicted, and now it is 90% predicted, which is still normal, but that patient has had a decline.

Dr. Noth: I think those are outstanding points. I think that really nails it, right? As we move forward here into the next few slides, we'll see that, of course, the pick-up on the HRCT [high-resolution computed tomography] is very, very high. We need to be picking it up, and then we need to be deciding who we're going to be concerned about. It's really both tools together giving us an example of what's going on from different angles. Right? The CT's really giving us that clear image of what's going on, but the pulmonary function tests help tell us whether or not the deficit is clinically meaningful, and to what extent and at what level it's progressing. So, one of the key elements, of course, is that CT scanning is progressing quite nicely in its ability to pick up on change over time, but we're not quite there yet. So, we really are dependent on those longitudinal declines in pulmonary function tests to tell us who's getting better and who's getting worse. I think all of that goes into those mortality prediction models and considering the probability of progressive disease in these patients.[1]



When we think about the HRCT as a screening tool, just as Dr. Volkmann laid out for you, this is what we want to use. This is going to be the most sensitive tool that we're going to have to pick up that underlying interstitial lung disease. The PFTs alone aren't going to pick up on it until it reaches a certain level of clinical significance that the test is going to be able to pick up. And so, relying solely on PFTs isn't going to tell you whether or not it's there.

One of the things that happens on this slide is that they quote the Bernstein study,[10] which shows that the PFTs lack that sensitivity in picking up the interstitial lung disease, because you're looking for an FVC of less than 80% of predicted.[10] And, of course, that's based off the notion that you're starting at 100, but patients…, the range for normal in patients is anywhere between 80 and 120. So, it's that loss relative over time that becomes the marker and why that becomes so important. They also recommend taking a look at both the FVC and the DLCO [carbon monoxide diffusing capacity] as different measures of different aspects of the lung

function, with the FVC representing the fibrotic portion of the exercise, and the DLCO—the loss of the capillary beds—that may result from that fibrosis or underlying pulmonary hypertension as a means of predicting the underlying element of disease.

Addressing Patient Burden

Dr. Volkmann: When we think about the level of burden on the patient, it tends to be pretty heterogeneous and obviously complicates the diagnosis and the treatment strategies. Obviously, these comorbidities, and the morbidities themselves related to the disease process, can be quite significant to the patient, and we always tend to focus on the most life-threatening first, but that doesn't mean we should be ignoring the rest of them. As you'll see moving forward, of course, renal crisis was really one of the major concerns, but as we've gotten better at managing that, interstitial lung disease has moved to the top of the list because, if they live long enough, this is where we're going to see their progression and their complications related to that interstitial lung disease in the setting of scleroderma.[2,5] So, we need to look for that lung involvement, above and beyond what's going on with the skin.

Now, something I learned from Dr. Volkmann at one of her lectures a few years ago is that the onset of that interstitial lung disease is approximately 4 to 5 years in after the initial diagnosis.[2] I think that's really very interesting and also very clinically important. Understanding when the onset of disease occurred probably will provide us with a heightened sense of when to screen and when to be worried. And, as I just mentioned, interstitial lung disease is now the number one cause of death in these patients, and they experience 3 times a greater risk of mortality when they have an underlying interstitial lung disease in conjunction with scleroderma.[6,8,11] Obviously, there then ends up being a higher prevalence of comorbidities, and those comorbidity outcomes occur at a higher rate than with scleroderma alone when seen in scleroderma with interstitial lung disease.

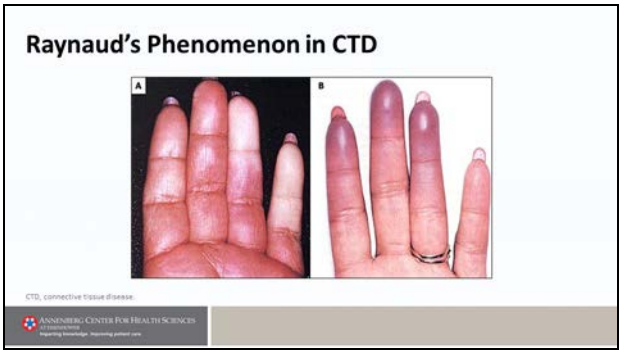
Clinical Features and Symptoms

Dr. Noth: Finally, the clinical features of systemic sclerosis. I feel like I'm stepping into Dr. Volkmann's territory, but I'll put them out there, then let her pick up cues from here. We see diffuse cutaneous skin involvement, nailfold capillary abnormalities and digital ulcers, pulmonary hypertension… Certainly, immunologic markers are what we use and start to screen with in these patients. Vascular damage and vasculopathy, extensive fibrosis of the skin, and internal organs and atrophy of the small arteries of the skin and internal organs that can result in irreversible damage.[3,6,12]

Dr. Volkmann: Absolutely, and one thing I'll add is that patients early on with diffuse skin disease may not have a lot of skin involvement. Early on, they just may have puffy hands or skin thickening of their forearms, and these are patients are still at risk for getting interstitial lung disease. In addition, our patients who just have limited skin disease where it never really progresses to diffuse disease, these patients also are at risk for interstitial lung disease; so, sometimes I see misdiagnoses when the skin disease is not apparent yet. And then there's this rare subset of scleroderma, sine scleroderma, where they won't have any skin involvement, but they'll have autoantibodies specific for scleroderma, and they'll also have things like interstitial lung disease.

You had mentioned capillaroscopy, and this is something, as rheumatologists, we rely on to examine the nail bed changes in our patients with connective tissue disease. And the reason why this is helpful is that things like Raynaud's phenomenon can occur in a lot of people—even normal, healthy people can have Raynaud's.

If we look at the nailfold capillaries, and we see changes, usually this can be a sign that the Raynaud's is associated with an underlying connective tissue disease, and in scleroderma, we see some of the changes that are represented here. So, you can see, in this example, the patient has some hemorrhages present. There's also some tortuosity of the capillaries. There's dropout. So, there should be normal, like, capillary loops, and if there's some dropout, that can be a sign. There's been some interesting work lately looking at nailfold capillary changes as predictors of severe organ involvement, including lung disease, and so there'll probably be more about this in the future. But, right now, we rely on capillaroscopy to determine whether that patient's Raynaud phenomenon is related to an underlying connective tissue disease.



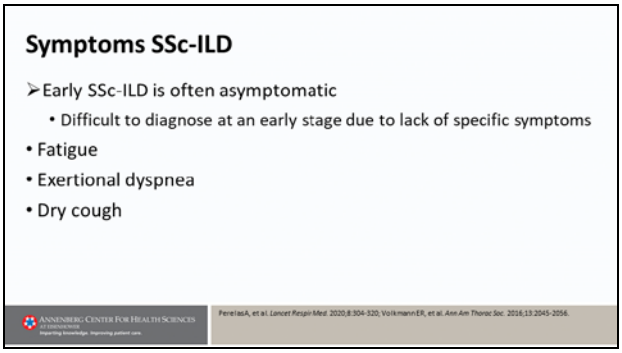
When we see Raynaud's as exemplified here, you can see these sort of different color changes in the fingers of the hand. So we ask patients, do you have changes like white or red or purple? Typically, these happen when patients are exposed to cold temperatures, but they can also happen not infrequently when patients are exposed to stressors, too. So, that's another possibility.

Other features, when we think about systemic sclerosis, we've talked about the lung manifestations, the Raynaud's, the skin, but in addition, patients can have overlap autoimmune diseases. They can have things like inflammatory arthritis or even rheumatoid arthritis. They can have inflammatory myositis, and this happens not infrequently in our patients. GI problems are a major cause of morbidity and even mortality in these patients; both the upper and lower GI tract can be involved. And when the upper GI tract is involved, patients can have bleeding. So, this could be from esophagitis or bleeding that occurs in the stomach due to vascular ectasias.[13,14] There can be a lot of esophageal disturbances, like difficulty swallowing and reflux disease, that can substantially affect patients' quality of life. I was curious, Dr. Noth, when you see patients with reflux disease, how do you think about that in terms of their underlying ILD?

Dr. Noth: What a fantastic question. I will tell you that it's a bit of a chicken and egg issue in that we don't know that it's directly related, but it certainly seems to be contributing at the very least. We know there's a certain amount of microaspiration that goes on. We know this for a variety of reasons, both measured in the actual barium swallows that we see, and we know that there's a change in the microbiome of these patients that seems to reflect what's going on in the gut. But what's intriguing to think about is if that's leading to the damage that then causes the fibrosis to manifest itself and shrink the lung further. It also causes the crux to the diaphragm to release and for the esophagus to be able to slide a little more freely, which then promotes the acid production. So, in fact, the underlying fibrosis may be leading to the increase in the reflux, as well, and you end up in a bit of a spiral. The nice thing is we'll be talking about it a bit later, but it's probably a comorbidity that's

important to treat, because we can really make differences, and most of the data—although there are no randomized, double-blind, placebo-controlled trials—would seem to suggest that there's a benefit for controlling the reflux.

Dr. Volkmann: We recently did an analysis of our own, the Scleroderma Lung Study 2,[15] which was a randomized, controlled trial. I think we're going to speak about it later. And in this study, we looked at patients' severity of reflux at baseline, and it actually was one of the strongest predictors of progression of their ILD radiographically over the course of the study, even when we controlled for our treatment arm assignment and baseline severity of lung disease. So, I do think it probably is important, but it's sometimes not clear, as you said, this chicken and egg issue, which comes first. So, thank you for sharing your thoughts on that.



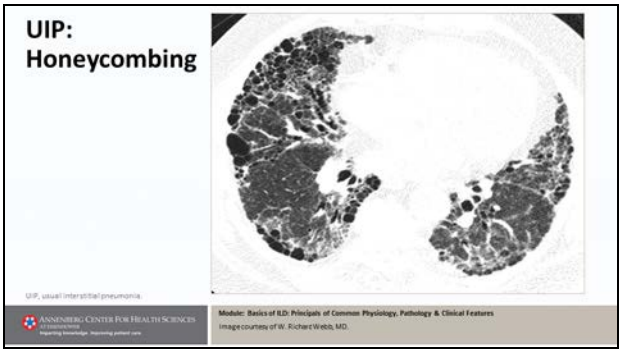
Early on, many of these patients—as we both mentioned—can be asymptomatic, or they may have modified their lifestyle to avoid feeling short of breath or avoid having a cough. And so, asking these very pointed questions about what you were doing 6 months ago that you can't do now, can be helpful. I also find it helpful to talk to caregivers or family members who may accompany the patient, because sometimes they have better insight into how that patient's lifestyle has changed, and they may say he used to always take out the trash and now our son is doing it. So, it's sometimes helpful to get this other information, too. And then, early on, even before shortness of breath, a lot of patients can just report feeling tired when they exert themselves. So, they don't say, I feel short of breath when I walk up the stairs, but they'll say, "When I get to the top of the stairs, I feel so exhausted I have to rest."

I think it's important to keep in mind that after dyspnea, the second most common symptom that we see in SSc-ILD is cough.[3,5] Cough can be a dry cough, but over the course of the disease, can become a wet cough, too. I would say this can be very troubling for patients, and, as a rheumatologist, it's not something I have a lot of training in treating. I'm curious to know, when you have your patients with cough, how you approach this issue? Because these patients can also have cough due to their reflux disease, as well.

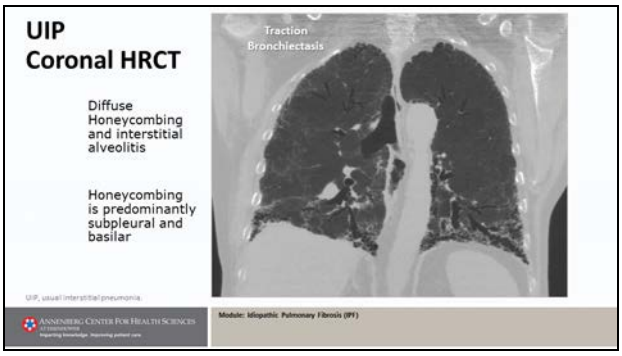
Dr. Noth: That's a fabulous question in regard to the cough, and the number one cause of complaint for patients with interstitial lung disease that I see in my clinic is that dry cough. So, several points. First, by far and away the most important thing I do for them is reframe that cough. They're all very concerned that the cough is a sign of the underlying disease, which it is, but it's a bystander, right? It's a result of the bronchiectasis and tortuosity that occurs in the larger airways that leads to that cough, and it tends to be dry, as you point out, early on because, frankly, it's got nothing to do with production until you develop signs of bronchiectasis, which are more pronounced with infectious overlay. And so the first thing I tell them is to worry less about the cough, and that the cough is a way of providing them with some relief for what's down there to help bring it up, and that it's a proper mechanism to keep them in better shape.

The second part is reassuring them and explaining to them that the treatments for cough are, unfortunately, incredibly limited. It's a billion-dollar industry, with very poor treatments, of which opiates are by far and away the most powerful element of controlling it. So, if the cough doesn't

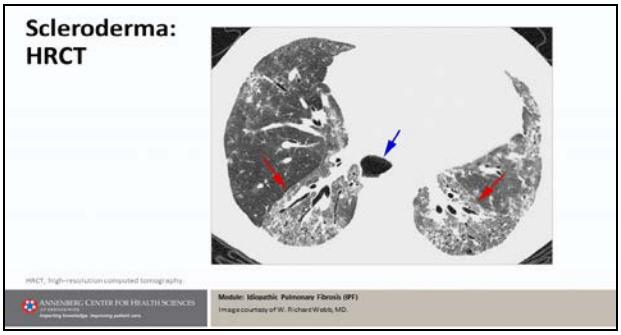
warrant an opiate, it's probably worth more to simply let the patient suffer through it and understand that it's okay to suffer through it, and that it's not infectious, and that it shouldn't scare anybody else.



This is representation of usual interstitial pneumonia. Now, probably most important is the name itself. It's the usual or most common type of scar pattern that we see. Radiology borrowed this from pathology over their findings, and the key features are really the honeycomb lung that you're seeing on this axial image. So, it's the small circles on the peripheral aspect of the lung that tend to be more basal than anterior, and on the periphery, and that they aggregate into looking like a beehive honeycomb. And that is the pattern recognition for this usual interstitial pneumonia pattern. It is the most concerning pattern we see in the interstitial lung diseases, because independent of the disease state, it's the one that is most ominous for progression and mortality.



I'm always super-excited to present this coronal image, and the reason is nobody ever looks at the coronal images. I think it really helps paint a picture for any practicing physician over what this disease looks like. When we see that usual interstitial pneumonia pattern, as I describe it, it's posterior basal, and the result of the fibrosis that surrounds it is that it pulls apart the airways. You see those honeycomb sections aggregate into pulling out the terminal part of the airways, and they are far larger than they should be. It's not difficult to appreciate that when you have this abnormal airway pattern, you develop a cough. Basically, gunk accumulates, and it needs to be brought up, and that's why coughing is a normal response in these patients. That's not to say it's not representative of the level of disease or that it isn't annoying to the patient as their number one complaint, but it is something that should be tolerated, and we want them to cough to clear this out. It's just a beautiful representation in how the upper parts are relatively spared compared to the lower parts.



Then we contrast that with this CT, right? Now we have a more ground-glass appearance. When we say ground glass, what we mean is the old Coca Cola bottles that used to get washed up on the sand on the beach, and you get this ground-glass appearance of scratched glass, and it represents basically water or cells as a very homogenous pattern that's throughout that portion of the lung. The red arrows are showing you the differentiation at lobe cut-offs over where that ground glass appearance is. If you squint really hard you can still

see some areas that might have some honeycombing, but really what it is, is ground glass with the septa of the alveoli forming ridges around it. And you still get that bronchiectasis pattern of pulling apart the airways, which leads to that cough.

Then, lastly, you've got that blue arrow. That's of the esophagus. So, one of the universalities in scleroderma, of course, is a loss of esophageal function at various levels, and you get this dilation of the esophagus, which leads to that reflux disease we were talking about earlier and that chicken and egg phenomenon, particularly in scleroderma, which puts them at risk for more fibrosis.

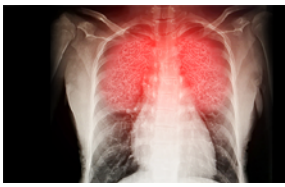
Dr. Volkmann: This is great. I'm just curious because rheumatologists don't often get a lot of training in CT assessment for lung diseases, and if, let's say we were encouraging rheumatologists to order a CT, are there specific ways you would suggest ordering the CT to be able to capture interstitial changes, especially early on?

Dr. Noth: What an important question. Yeah, there are a series of them. So, first and foremost, the good news is that modern CT scanning has made this a little easier. We want a high-resolution scan, and that's really important because this ground-glass appearance will be very different if you're looking at a 5 mm thickness cut or a 1 mm thickness cut, right? With 5 mm, you're aggregating the information across that 5 mm. So, things that may not be ground glass are going to look like ground glass only because it's thicker. So, it has to be a high resolution. And then we want to get prone, supine, inspiratory, and expiratory, and the reason is we're looking for the dynamics of the lung and the change in shift. If these changes are related to either atelectasis or water, when you flip the patient from prone to supine, you're going to get a change in the imaging that you're going to see suggesting that it wasn't actually the tissue itself. And inspiratory and expiratory will help you discern if there is air trapping going on, or mosaic pattern related to obstruction, or loss of vascular beds. And all of that becomes highly informative over the nature of the disease. What's really important to understand in the interstitial lung disease as a whole is that CT scanning has practically supplanted the biopsy as the guiding tool for diagnosis and the reason is we get the entire image.

ESSENTIAL EARLY SCREENING

Dr. Noth: Finally, we have the importance of early screening, right? So, as we pointed out earlier, we know that the onset's going to be more in the early years, in year 4 to 5.[1] So, that's the best target spot. And then we talk about identifying it effectively, and that gets at what we were just talking about, that ensuring that we want those prone, supine, high resolution, inspiratory, expiratory images.

Now there's a note here in regard to the radiation exposure, but as a colleague of mine once put it, the radiation exposure from a CT scan is no worse than flying in an airplane during a solar flare. The reality is if we need the CT scan, we ought to be getting the CT scan and not worry about the radiation exposure. What's interesting is that there are new modalities coming up that probably are allowing us to get at it a bit with things like lung ultrasonography as an alternate approach. During bronchoscopy, it's not mentioned here, but there's new colposcopy methods that take a look that way as well. We obviously want to use these when we have any concern that there might be an underlying interstitial lung disease, even in the absence of clinical symptoms, because hearing things like fine bibasilar crackles on auscultation is almost assuredly going to direct you towards a positive CT scan. Now, we want to have early detection in those patients so we can make better therapeutic decisions.



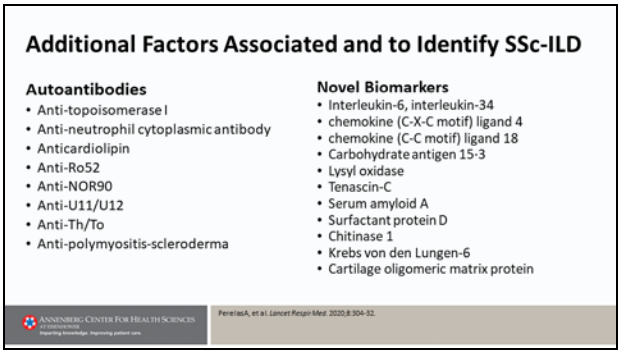
SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE: MAKING CONNECTIONS, ELEVATING CARE

RISK FACTORS FOR SSC-ILD AND ASSOCIATED COMORBIDITIES

Dr. Volkmann: I'd like to share with everyone a second case vignette. This is a 58-year-old African American male who presents with progressive lung complications and reports recent numbness in toes and fingers. His primary care physician is in a quandary about what are the best next steps. And I think, when I see a patient with SSc-ILD, I consider their risk factors not only for developing ILD, but their risk factors for developing this progressive phenotype. We know from a number of clinical trials, both observational studies as well as clinical trial cohorts, that [there] are specific features of patients who predict this progressive phenotype. And this patient has a couple of them.

RISK FACTORS FOR SSC-ILD

He's a male patient, that's a risk factor for increased mortality. He's also African American, and this is also associated with increased lung disease and mortality in scleroderma. Age is another important factor, so increased age associated with worse outcomes with SSc-ILD, as well as diffuse disease, a greater extent of lung disease on HRCT, reduced DLCO, and FVC at baseline,[3,7,16,17,18] and then the other part I look at is their autoantibodies. I think this is incredibly important early on in the course of the disease to establish. So, for example, if the patient has the Scl-70 antibody or anti-topoisomerase I antibody, this is associated with having a more progressive ILD phenotype. So, this is a patient, even if they come to me and they have a normal FVC or DLCO, if they have this Scl-70 antibody, I'm following them very closely because I know that they are likely to progress over time. And this would contrast with someone, let's say with a centromere antibody, which patients typically, with the centromere antibody, will have more mild ILD or no ILD; but if the ILD is present, it's typically not very progressive.[3]



Other factors, in addition to these autoantibodies—there's a long list here—and I think the ones for the audience that are important to remember, so the Scl-70 or anti-topoisomerase I is probably very important. There's evidence that anti-Ro52, this is also called SSA, this can be associated with a more progressive ILD phenotype as well as Th/To. And then keep in mind this last one, the anti-polymyositis-Scl—it's sometimes abbreviated as PM-Scl—is associated with this myositis overlap. Sometimes these patients can have ILD that's more characteristic of a myositis ILD, so they may not just have NSIP, but they can have organizing pneumonia too.

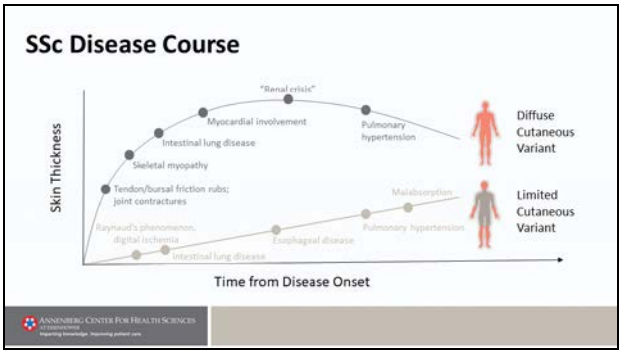
Lastly, there are some novel biomarkers that are under investigation in studies to be able to predict these different phenotypes. So, for example, IL-6 is one where higher levels of IL-6 are associated with increased progression of ILD. I'm curious, Dr. Noth, whether you have any insight into some of these biomarkers, or if you've used them at all in your practice to help risk stratify your patients?

Dr. Noth: It's one of those things that it's not been quite ready for prime time, if you will, but they are fascinating for a variety of different reasons, and they overlap on many of the interstitial lung diseases. So, of course, the KL-6 [Krebs von den Lungen-6] is really an epithelial mucin marker and has been demonstrated in both HP [hypersensitivity pneumonitis] and pulmonary fibrosis, as an example, as has the surfactant protein D, and the lysyl oxidase 2 was a target for

therapy. And so, I think we're going to see that. We're going to start using these as they integrate themselves more into clinical trial successes, right? So, as Scleroderma Lung Trial 3[19] were to use them, or frankly the antifibrotic trials that have been moving forward use them, more and more will then have an opportunity to make an impact.

Multiorgan involvement

Dr. Volkmann: Systemic sclerosis is a multisystem disease, and what this means is that it can affect multiple different organ systems. So, the most common organ system that's involved, and affects 95% of patients, is the skin. After this, the next most common organ system affected is the GI tract, followed by the lungs—the topic of this talk—and then the heart can be involved, as well as the kidneys and musculoskeletal system.



The organ involvement in scleroderma typically occurs at different phases of the scleroderma. So, if we look, for example, at a patient with diffuse cutaneous disease, from the time of disease onset, usually their peak amount of skin thickening occurs within a couple of years. And then over time, even in the absence of therapy, the skin will start to soften. And then, when we look at the specific organs that can be affected along that time period, usually interstitial lung disease occurs early on, within the first couple of years. The GI involvement also occurs early on, and then patients with diffuse skin disease, heart involvement, kidney involvement also usually occurs within that first 4 to 5 years. Later, beyond that time point, is when we typically see problems with the lower GI tract, so patients can have a lot of distention, constipation, and then we can also see issues such as pulmonary hypertension. Again, this typically occurs later in the course of scleroderma.

Multiorgan involvement: Skin

Dr. Volkmann: In terms of the skin involvement, we categorize patients based on the extent of their skin involvement, so whether they have diffuse or limited skin disease. Part of the reason we make that distinction is because the evolution of the skin disease can be quite different. So, in a patient with diffuse skin disease, typically this patient is developing Raynaud's phenomenon and then, within 1 to 2 years, is starting to develop severe thickening of the skin. And it will extend beyond the elbows proximally, beyond the knees proximally; it can affect the chest or the abdomen. And this contrasts with a patient with limited skin disease, where they'll only have involvement from their elbows down, knees down and neck up.[20] In these patients, the timing or the evolution of the disease is a bit slower. So, they can get Raynaud's phenomenon, but then it may be 5, sometimes 10 years, before they start to develop skin thickening. This is the main reason why we make this distinction, because, again, keep in mind, both subtypes can get internal organ involvement, such as interstitial lung disease.

Multiorgan involvement: Gastrointestinal

Dr. Volkmann: We've talked a little bit about GI involvement and its relation to ILD, but I would say that this is something that bears mentioning because it's a leading cause of morbidity in these patients. They can often have uncontrolled reflux symptoms that not only affect their lifestyle, but even their sleep. So, patients sometimes have to sleep with a wedge, or even sleep sitting upright, to avoid having nighttime reflux symptoms. It's a common cause of cough; it affects 90% of patients; and, again, whereas it can affect any part of the GI tract, the upper GI tract is affected in most

patients. And GI symptoms can be exacerbated when there is ILD involvement.[21,22]

Dr. Noth: If I can interject on that one for a second. I was going to make a comment that one of the interesting things about the GI involvement is we did a study a few years ago looking at Nissen fundoplication, which seemed to suggest a modest improvement in the FVC that was preserved over time. But great caution should probably be had, and great thought when doing it in scleroderma patients because, of course, that level of esophageal dysfunction on top of that reflux makes the Nissen that much more complicated to do. And they end up necessitating partial wraps instead of full wraps in order to be successful. But it really does link back to what you were pointing out earlier, which is unfortunately when you think about transplanting these patients, it also complicates their transplant courses because we know that they get a higher rate of rejection if we don't do the Nissen. So, it becomes a tough thing to deal with.

Multiorgan involvement: Lung

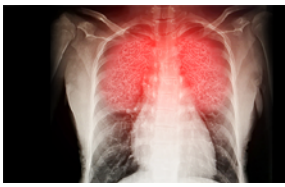
Dr. Noth: Let's talk a little bit about the lung involvement in this instance. So, when we say that lung fibrosis occurs in 80%, what we really mean is that, of course, the HRCT is going to pick up some level of fibrosis in these patients in upwards of 80% of the cases. And when we look at the clinical manifestations in these patients, the ones that we pick up by pulmonary function tests because they have symptoms, interstitial lung disease will occur in about 25%-30%, and a lower number, 10%-12%, will have manifestations of pulmonary arterial hypertension.[23,24] I really find it fascinating, you were talking a bit earlier and I can never quite keep it straight in regards to the relationship to the autoantibodies, but I remember that the Scl-70 is predominantly the interstitial lung disease pattern, and then I worry, of course, when it's not the Scl-70, that you're going to see the pulmonary hypertension as the more predominant component.

That's important because we see that as an independent driver for mortality in these patients when they get severe pulmonary hypertension. And we've already discussed that the interstitial lung disease itself is now upwards of 60% of the scleroderma-associated mortality, which we're seeing in the modern era, particularly in those with a more rapid progressive course. And, of course, as the innocent bystander, if you will, for systemic disease process, we expect to see it in other involvements above and beyond the lung. And so, we get a connection between other organ involvement and the lungs.

Multiorgan involvement: Cardiovascular

Dr. Noth: One of the major things to be worried about is the cardiac involvement. We see an equal incidence in males and females, so while this is a female-predominant disease, it isn't showing any favoritism by gender when you see the cardiac components. And, of course, we see it more in older patients with higher incidence rates, and it seems the diffuse skin involvement patients have a higher incidence rate as well. And then back to that question in regard to the autoantibodies: the anti-topoisomerase-I autoantibodies are a risk factor for that cardiac involvement in patients with scleroderma.

What's fascinating is that we're mostly seeing a diastolic dysfunction as the biggest presenting form and, again, while there are no sex differences there, we are seeing a difference by age with the diastolic dysfunction more prevalent in older patients than younger patients. And it's influenced over time by whether or not there's skin involvement, and so patients with diffuse disease end up with a 2.1 higher incidence rate for an underlying diastolic dysfunction.[22] Unfortunately, we do see some levels of cardiac arrhythmias as well, and those can be fatal in patients with scleroderma cardiac involvement.



SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE: MAKING CONNECTIONS, ELEVATING CARE

Multiorgan involvement: Kidney

Dr. Noth: Finally, what was probably the biggest concern for the longest time was renal involvement. We knew that administration of glucocorticoids in these patients increased the risk of renal crisis. That, of course, was greatly concerning and led, with cardiac complications, and more rarely, when we saw pulmonary restriction. But when we saw elevated systolic pressures, the pulmonary arterial hypertension, that was obviously a great concern, and, of course, in renal crisis itself. And so, prior to the advent of ACE inhibitors, renal disease was the greatest risk and the worst prognostic sign in patients with scleroderma for mortality.

Dr. Volkmann: It's interesting because I often get asked about some patients with scleroderma who, need to get corticosteroids for other reasons; maybe they have inflammatory arthritis or myositis, and I think that's important to note that the patients who get renal crisis are typically these diffuse scleroderma patients early in the course of the disease. So, in those patients, it's most risky to use these steroids. Later in the course of the disease, it's much less risky, so if they need to be used, it's usually okay. But this is a common question that I get as a rheumatologist. I just wanted to mention it here.

Dr. Noth: No, I think, I think it's why I probably never see it, right, because I always end up on the tail end, after they've had it for some time, and the interstitial lung disease has been picked up. But I do think the key is that we're better managing these things.

Multiorgan involvement: Musculoskeletal

Dr. Volkmann: Many patients can have musculoskeletal involvement, in whom scleroderma and inflammatory arthritis is common. I would also say, because a lot of times scleroderma affects patients in their older age, osteoarthritis can happen too, and sometimes we have to distinguish between the 2. Patients can get joint contractures, and this can happen due to the tendon thickening. Often it can occur in the hands, and this can affect patients' hand function. So, we typically recommend occupational therapy. And then myopathy is something important to consider. Early in the course of scleroderma, particularly in patients with diffuse skin disease, they can have elevations in their CK [creatine kinase] or aldolase, and it's usually a mild elevation. The CK would be in the 500 to 1,000. This we think of as being more of myopathy related to scleroderma. It's different than a true overlap myositis where we see CK levels in the 10,000 to 20,000 range. So, the myopathy of scleroderma typically occurs early on in a patient with diffuse skin disease.

Multidisciplinary Approach

Dr. Volkmann: This condition affects multiple organ systems. I have found it particularly helpful to try to engage with other specialists to really embrace this multidisciplinary approach. This is not a disease that I manage just all on my own. I rely a lot on pulmonologists, like you, GI doctors, cardiologists, sometimes dermatologists, and providing this comprehensive approach can be really helpful to the patient. I'm curious, in your center, how you apply this multidisciplinary approach, too.

Dr. Noth: You nailed it right on the head! It absolutely has got to be a multidisciplinary approach to be successful. We all take a different level of ownership, if you will, depending on which way the patient came through, but it's such an advantage to the patient, because it gives us the opportunity to weigh in with far more depth. An example, when we read the pulmonary function tests for subtleties that we may be picking up, which otherwise would be ignored. The flip side, obviously, is in the joint and skin comorbidities that come up as, you know… if they present for treatment, and then, frankly, we tend to share the visits. I have one clinic where we do it as a…the pulmonologist and rheumatologist have clinic at the same time, which we organized intentionally

for that purpose to concentrate on these patients, but there are others when we can't do that, [so] we alternate the visits. And when we get to treatments, that offers a real advantage because we can do it a little further apart while still maintaining the level of monitoring that's required for those patients with their regular visits.

Addressing comorbidities

Dr. Volkmann: I think, in addition to the multiorgan system aspect of this disease, there's also a lot of comorbidities that can occur unrelated to scleroderma but need to be addressed by a specific specialist. We've talked about Raynaud's phenomenon, and this can become severe, and patients can have digital ulcers, and so sometimes we're involving vascular surgery in cases. We've talked about the reflux disease. Patients can frequently get upper-respiratory tract infections, and this might be related to the treatments we use that suppress their immune system, as well as their abnormal lung architecture. Type 2 diabetes can occur, particularly in our patients with steroids. COPD, arrhythmias,[22,25,26] and we've talked about some of these other things, too. I'm curious, when you consider your patients, how do you assess for these comorbidities?

Dr. Noth: I've been a big fan of going after the comorbidities for ages, because we had such limited therapies for so long. Any practicing physician, I think, quickly realizes that if you take care of some of these, you really make a big difference to the patient. And so, it's more opening salvo, when I see them on their first HP, is really what are the levels of these comorbidities, and then it's a continuous exercise as they come through on their regular follow-ups.

Dr. Volkmann: Right. And I think, in general, we want to treat these patients as a whole patient. So, you're not just addressing their scleroderma manifestations, you're managing their comorbidities and again, I think, in a lot of these cases, we want to intervene early. You know, even with things like sleep apnea, which can again happen in these patients, [and] can cause a lot of daytime fatigue that might be difficult to distinguish from their autoimmune disease. If we identify this early, we can intervene and potentially improve this patient's quality of life.

CURRENT AND EMERGING TREATMENT FOR SSC-ILD

Practice guidelines: Past, present, and future needs

Dr. Volkmann: There's a lot of unmet needs in the space of scleroderma and scleroderma ILD, in particular, and one of them is practice guidelines. This is something that's a really evolving area of research and interest to a lot of us around the world. There were guidelines developed in 2013 between the American College of Rheumatology and EULAR [European Alliance of Associations for Rheumatology], which is a European association.[27,28,29,30] These guidelines are somewhat outdated, because they are 2013. They're a little bit antiquated, and they don't consider treatments that have been developed since then. We've actually had 2 recent approvals for therapies for SSc-ILD in the last couple of years. I definitely think there's an unmet need for developing practice guidelines in this space, much like you've done in other pulmonary diseases, to a greater extent than we've done in rheumatology.

There is a European consensus statement that was recently published regarding management algorithms,[27] and a big part of this was that everyone agreed that all patients with SSc-IL, with SSc in general, should be screened for ILD, and the HRCT is the primary tool for diagnosing this. The PFTs were felt to be supportive for screening and diagnosis, and they also felt it was probably appropriate to treat in severe cases, but no pharmacological treatment would be an option for some patients. And these would be patients, potentially, who did not have symptoms, had normal pulmonary function, and didn't possess these risk factors for having this progressive

phenotype. But I think, again, this consensus statement really needs to be elaborated on in terms of integrating treatment options, since we do have a lot of different options available to us now.

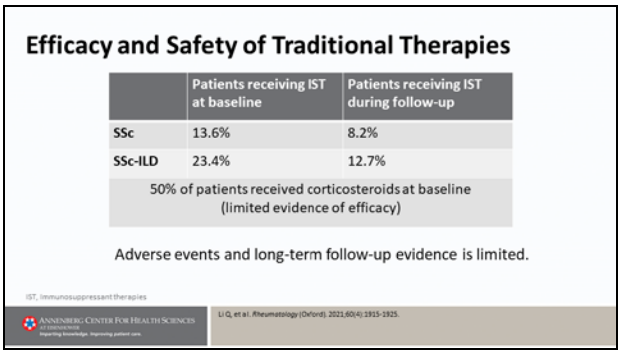
Whom to Treat Upfront

Dr. Volkmann: The question is really whom to treat upfront. It may not be necessary to treat these patients with stable disease that's not progressing, or even these patients we have who have had ILD for a decade, and it's not progressed—these are patients you might be able to monitor closely. But I would say that I tend to treat these patients early on because I'd rather not risk them losing lung function, because oftentimes that's an irreversible process, and I'd rather not wait for that patient to become symptomatic before treating. How do you approach, how to start treatment in your patients with SSc-ILD?

Dr. Noth: I think you raised some terrific points. It's because they are younger than our IPF [idiopathic pulmonary fibrosis] patients, the rules of engagement, I think, are a little different. I always tease that you have to approach this differently in a 40-year-old than you do in an 80-year-old, right?

The preservation of lung function is just much more important in this patient population than what we're doing in the IPF patients. The rheumatology field's done a fantastic job of taking a look at the therapies that are out there to demonstrate that preservation and, frankly, even some reversal of that ground-glass appearance that we saw on that CT scan. And so, I think I'm a little more aggressive in the scleroderma patients than I am in the IPF patients, because of their age and the availability and the effectiveness of the treatments.

Dr. Volkmann: This was interesting, looking at the efficacy and safety of traditional therapies in patients receiving immunosuppressive therapy at baseline and those who received it at follow-up.



You can see that among those patients with SSc, fewer patients compared with those with SSc-ILD were receiving immunosuppressive therapy. And that during follow-up, that gap narrowed. Fifty percent of patients received corticosteroids at baseline,[25] but we really don't have long-term follow-up on these patients, right? This is just based on reporting of data, but it doesn't really give you insight into outcomes, such as mortality or progression of disease.

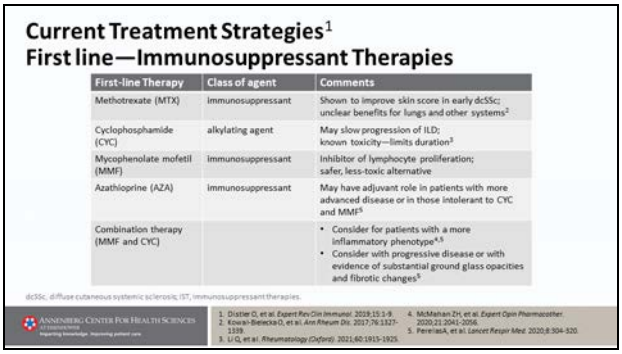
Dr. Noth: I was going to ask, do you think that these low rates represent where these patients are on their timeline, because you so nicely presented earlier that there seems to be a period of greater activity for these patients to where they're leaning towards monitoring instead of treating?

Dr. Volkmann: I think that's possible, and I also think, though, there's this general reluctance in time to treat these patients until they become severe. And it's interesting because it's different than other areas of rheumatology. So, for example, when we see patients with lupus, if they have a little bit of protein in their urine, and we diagnose them with nephritis, we treat them right away with immune suppression. We don't wait until they have kidney failure and a rising creatinine to treat them. I think in scleroderma it's a little bit different. Sometimes there's this mentality, well let's wait and see if their lung function declines, and then we'll treat them. And I think we need to move away, since we have therapies now, and

maybe start them sooner to help prevent progression.

Immunosuppressant Therapies

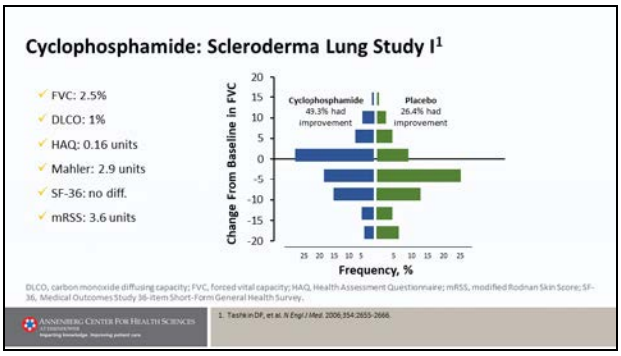
Dr. Volkmann: When we think about the immunosuppressant therapies used, here are a list of some of them that are used throughout the world.



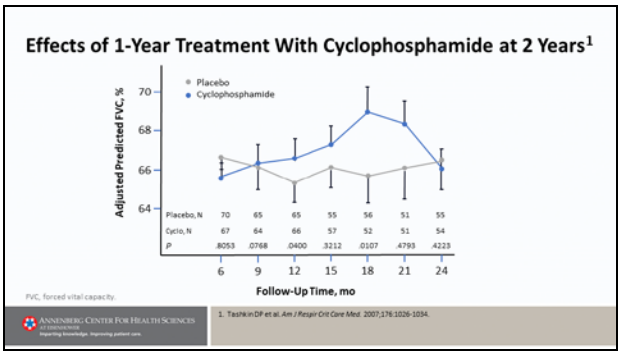
Methotrexate, this has been used more historically. Cyclophosphamide [is] also used more historically and somewhat toxic. And then mycophenolate, which I would say is probably the most commonly used agent for treating lung disease in scleroderma, particularly in the United States. Azathioprine is sometimes used[20,28,31]—I see this used a lot by pulmonologists. And then sometimes combination therapy is needed, as well. And again, these agents all have been demonstrated in specific studies to have effects on skin and lung disease.

Scleroderma Lung Studies

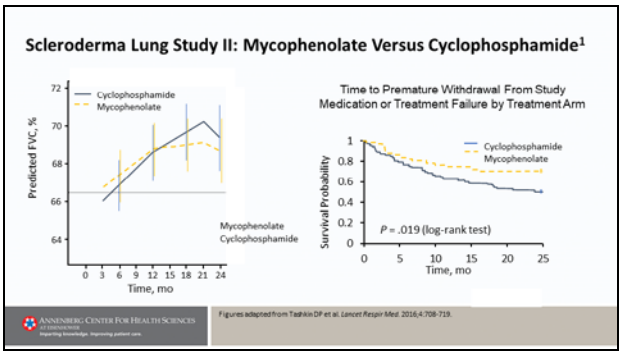
Dr. Volkmann: One example would be the Scleroderma Lung Study I.[32] this was an NIH-sponsored, randomized, controlled trial conducted at 13 centers throughout the United States, and it compared 12 months of oral cyclophosphamide with 12 months of placebo. What we learned in this study was that the patients who were randomized to cyclophosphamide, about half of them had an improvement in lung function, whereas, in the placebo arm, only about a quarter had improvement.



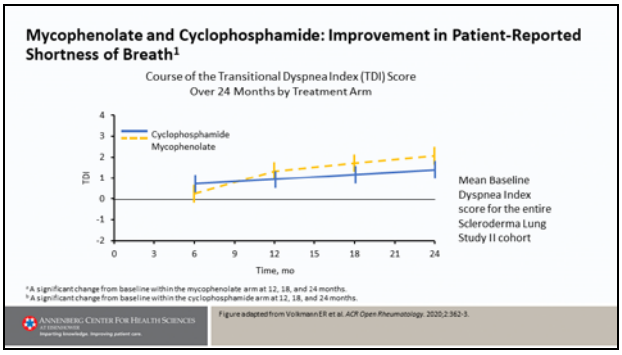
In addition, the cyclophosphamide arm was also associated with improvements in how a patient felt; so, their health assessment questionnaire, their Mahler dyspnea index…, so shortness of breath or SF-36, as well as their skin score.



The very interesting thing about this study is that patients were followed for an additional year off therapy, and what they found was, in that additional year off therapy, those patients who had been randomized to cyclophosphamide actually had a deterioration in their lung function over that year off of therapy and were essentially back to their baseline. This taught us that probably 1 year of immunosuppression is not sufficient for leading to a sustained improvement in lung function in our patients with SSc-ILD.



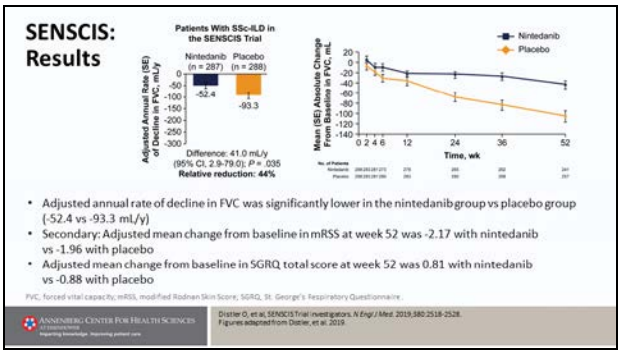
This was really the rationale then for the second scleroderma lung study, the Scleroderma Lung Study II, which compared 24 months of oral mycophenolate with 12 months of oral cyclophosphamide followed by 12 months of placebo.[15] You can see that the forced vital capacity actually improved in both treatment arms, and there was no significant difference in terms of treatment efficacy between these 2 arms. However, the way these 2 treatments really differed was in their safety and tolerability. So, not surprisingly, the time to premature withdrawal from study medication or treatment failure was much greater in those patients who received cyclophosphamide compared with mycophenolate. I think this is why we typically go to mycophenolate over cyclophosphamide due to these safety and tolerability concerns.



I'll just mention that we get hung up a lot on things like the FVC and the DLCO, but what really matters to patients is not so much these numbers, but how they feel and function. So, I think it's important in the studies we do to look at measures of this, and so, in the Scleroderma Lung Study II, we found that the transitional dyspnea index, which is a valid measurement of dyspnea, improved in both treatment arms with no between treatment arm differences.[33] So again, I think it's important to consider quality of life when we're evaluating treatments for these patients.

TARGETED TREATMENT: ANTIFIBROTIC AGENTS

Dr. Noth: This is a completely different approach, right? You did such a marvelous job of going through the immunosuppressives, and, of course, they are immunosuppressives. They really are trying to target the root of the injury, if you will, in scleroderma. The thing about the antifibrotics is when they first came on the scene, the pulmonary community teased they may work in the kidney for all we know, because they're really targeting an end-stage fibrotic process that's organ-independent. And so here we're showing the first one, the antifibrotic agent nintedanib, which is an oral targeted tyrosine kinase inhibitor. It's often referred to as a triple kinase inhibitor. The reality is it blocks 60-80 different kinases because it's a small molecule with probably a reiterative approach in its blockade,[34] if you will. It can be considered as first line among patients with a predominantly fibrotic pattern on CT scan,[3] and they successfully were able to demonstrate that it worked in the SENSCIS trial, looking at 576 patients at the rate of decline in the FVC.[35,36,37]

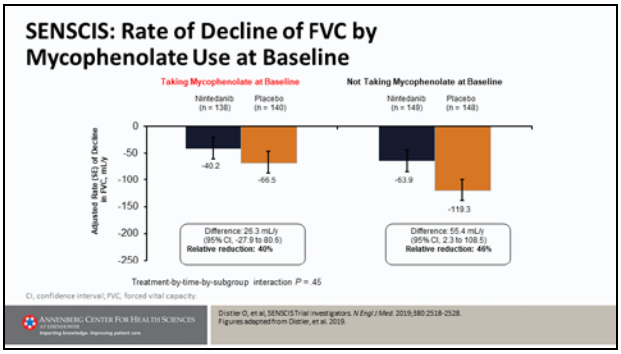


You made some great points in regard to the sense of shortness of breath being the most important to

the patient. From the FDA's perspective, it's what endpoint they were able to demonstrate. So, the FVC really becomes their measure, which is where the original nintedanib studies were conducted. And so in the SENSCIS trial, we see a reduction in the rate of decline over a 1-year period in the FVC from 93 mL loss to 52.[35] This is a pretty good mirror of exactly what we saw with idiopathic pulmonary fibrosis, roughly a 45% reduction in the rate of decline.

Now, what's important to note is the limitation of this class of drugs. It is a dramatic reduction in the rate of decline, but everybody declined. Everybody got a little worse with time. It's just that if you took the medication, you got a whole lot less worse than the group that wasn't taking the drug. And that was reflected in a change in the St. George's Respiratory Questionnaire, which is really a COPD questionnaire, where most of the domains are apropos to pulmonary fibrosis, but not all. Then a difference in the mRSS [modified Rodnan Skin Score] scale, as well over the 52- week period.

What was a fascinating question that immediately came up was because of the Scleroderma Lung Studies, mycophenolate is really the first-line therapy, and I loved your point about the azathioprine among pulmonologists. The truth is that's what we start in the field because our early studies used azathioprine. I personally use mycophenolate more because of the side-effect profile difference and ease of use. And it's why it's so important to have this multidisciplinary approach, because often I'm reaching out to find out, in a particular connective tissue disease, if there might be a more apropos selection of agent(s) beyond the repertoire that I'm comfortable with.



What this slide shows in the SENSCIS study is when they broke out the patients taking mycophenolate from those not taking mycophenolate, you're still getting the same reduction in rate of decline: 46% in those not taking the mycophenolate at baseline vs 40%.[35] While it looks like the benefit is a whole lot smaller at 26 mLs vs a difference of 60 mLs, it's really that relative rate reduction that's consistent. And before you ask whether or not 26 mLs is important, it's not important in year 1. It's really important in year 10, because if it's 26 mLs per year, that's 260 mLs over that 10-year period, and the difference between the 26 mLs on or off the mycophenolate is a 60 mL difference. That translated into a meaningful difference that the patient's going to functionally appreciate. So, this was part of the evidence base, to say, okay, we can use this in combination, and it's still giving us a benefit.

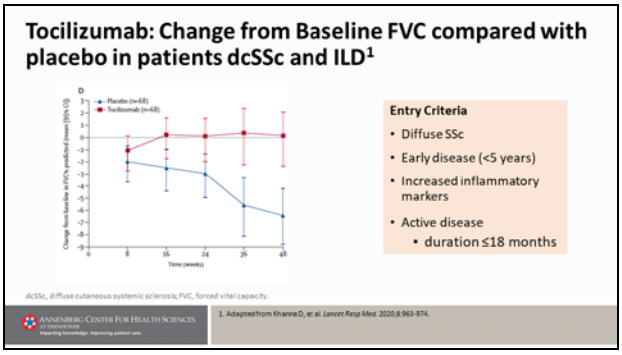
Biological Agents

Dr. Noth: What's interesting as you start to move beyond, into other biologic agents—really more into your territory—I'm going to make a couple of comments, but then I want to hear your opinion on these, as well. We were very interested in rituximab in ILD, in general, and so we end up using it in scleroderma cases, which is more granulomatous, and it seems to have a better clear response there. But there is a small, randomized, controlled trial showing that it may improve lung function in scleroderma[38] as well, making me wonder about the overlap in the mechanisms involved. And then the tocilizumab, which of

course has gotten so much attention because of COVID, is an anti-IL-6 receptor antibody but may have some effect here, as well. It seemed if the primary skin fibrosis endpoint was not met, but the secondary endpoints were, in preserving that lung function in these patients with early scleroderma ILD and in the elevated acute phase reactants.[24,30] I would love to hear your point of view on it.

Dr. Volkmann: In terms of rituximab, this is often something that I use as a second-line agent in patients who are having progression of their lung disease despite treatment with mycophenolate. And while there haven't been any very large, randomized, controlled trials on rituximab for SSc-ILD, there has been some work done looking at the EUSTAR cohort, which is an observational cohort of hundreds of patients in Europe with SSc-ILD. In that cohort, they looked at patients who had refractory disease who were put on rituximab and then compared them to matched controls, and they found that those who were put on the rituximab had an improvement in their lung function compared to the matched controls who were not.

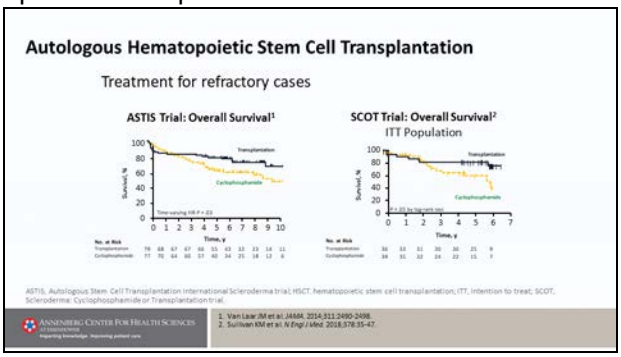
There is a randomized, controlled trial going on right now, a phase 3 trial in the UK comparing rituximab to cyclophosphamide for CTD-ILD, and many of the patients in this study have SSc.[39] So, hopefully, we'll get some more information there.



Then as you pointed out, the tocilizumab story is very interesting, and this was a study that was primarily designed to look at tocilizumab's effect on skin disease in patients with early diffuse systemic sclerosis with active inflammation, so elevated inflammatory markers like the ESR and CRP. And they found that it didn't meet its primary endpoint, as you said, but then when they looked at FVC change over the course of the study, they found that those patients randomized to tocilizumab did not have a decline in their FVC whereas those who were randomized to placebo did.[24] This led to the approval of tocilizumab for slowing the decline in lung function in patients with Ssc-ILD. So, this is an agent that I consider in patients who have early disease, active inflammatory markers, and who also have diffuse cutaneous disease.

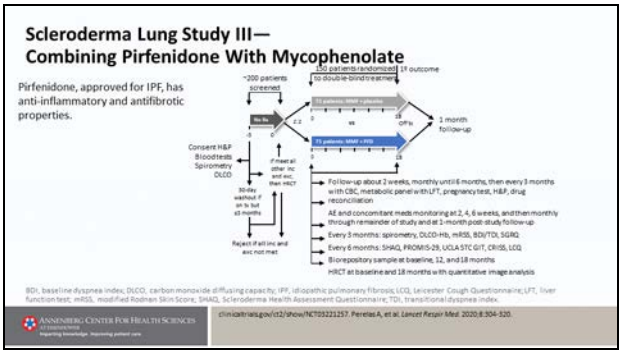
AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

Dr. Volkmann: We do have autologous hematopoietic stem cell transplantation as an option for our patients.



Typically, this isn't our first choice because this is a pretty intense procedure. It has to be done at an experienced transplant center, and it is associated with peri-transplant period mortality, mostly due to infections from cytopenias. But there were 2 large, randomized, controlled trials that were done: the ASTIS trial, which was a European trial and the SCOT trial which was a US trial.[40,41] In this study, the comparator arm was treatment with cyclophosphamide. You can see that over the course of 10 and 7 years, respectively, there was a clear survival benefit that was sustained in those patients who did the transplant.

I would say this is something to consider in patients with early disease. Typically, all these patients in these studies had diffuse disease, some internal organ involvement, and they probably failed another treatment.



Then, lastly, you had mentioned the Scleroderma Lung Study III, which I think is a really novel study design, because unlike the SENSCIS trial, which did not randomize patients to mycophenolate or not, this study actually treats all patients with mycophenolate, and then patients either receive pirfenidone vs placebo.[3,19] And it's really getting at the question: does upfront combination therapy with an immunosuppressive and an antifibrotic lead to a faster improvement in lung function than just using immunosuppressants alone? And I'm wondering, Dr. Noth, if, in your practice, do you ever upfront combine these therapies, or do you more sequentially add them on?

Dr. Noth: It's just a practical issue. I often do it sequentially, and the reason is with its side effect profile, right? So, it's just easier to be able to manage the medication; if I let them get on it for a month or 2, and it doesn't matter which one, obviously, I start with. Often that depends on accessibility. But it's just way easier to be able to put them on, let them adjust to the dosing regimens. What goes a little unsaid about the antifibrotics is that their dosing regimens do require some active management. You know, there is a need given that pirfenidone is 3 times a day, and nintedanib is twice a day, and both have a certain amount of GI upset. To control for that may have slightly different side-effect profiles that are reasonably well-tolerated, but they do require some active intervention.

"Pearls and Pitfalls" for Immunosuppressive Therapies

Dr. Volkmann: As a rheumatologist, I use immunosuppressive therapy to treat patients with a variety of autoimmune diseases, and so, as we've talked about in systemic sclerosis-related ILD, we often start out using mycophenolate therapy. I would say that what I've learned about using immunosuppressive therapies is that if you use them as monotherapy, oftentimes patients do not develop serious opportunistic infections. It's really when you start to combine immunosuppressive therapies that you really heighten the patient's risk of developing opportunistic infection. So, if you start combining something like mycophenolate with a biologic drug, like rituximab or tocilizumab, that patient is now at greater risk of developing infection. All this means is that you really want to monitor the patient closely. So, if the patient tells you that they have cold symptoms, a fever, low-grade; if they weren't on immune suppression, you'd probably just say, okay, well let's see how you do over the next couple of days and check back in. But, in a patient who's on immunosuppressive therapy, if they develop a fever, cold-like symptoms, we usually have a lower threshold for treating them with things like antibiotics, for getting imaging of the chest to make sure they're not developing a pneumonia. We're a little bit more aggressive about managing things. So, I think when you use immunosuppressive therapies, it's very helpful to have more vigilance for looking for infections and particularly when you're combining immunosuppressives together.

"Pearls and Pitfalls" for Antifibrotic Therapies

Dr. Noth: Along the same lines, when, the antifibrotics are really a new class of agents, and they're only 5 years old, having hit FDA approval in

2015. It's been a learning curve, and in a lot of ways, I think oncology's been giggling at us because we don't tend to suffer the same level of patients that they do, so commonly used in the chemotherapy agents. The antifibrotics have slightly different, but also overlapping side effect profiles, and that's made them a little difficult for patients to be able to tolerate. And the biggest thing, by far and away in the case of nintedanib, is, frankly, diarrhea. And you can imagine that for a pulmonologist to have to worry about diarrhea among its treatment regimen is not something we commonly deal with, given that we mostly give inhalers. Now, you know, both, some of the immunosuppressants clearly do, with their roots being in the chemotherapy realm, but the truth is that a little Imodium actually goes a long way at being able to manage that. And the understanding of the expectation on the part of the patients, it really does get back to their education. And so what we found is that these drugs are incredibly well tolerated when we prep the patients.

When we let them know that that side-effect profile will be there. We know that discontinuation of the agents from the clinical trials is at about 5%. So, we're able to successfully administer them in 95% of the cases, and that's on a drug that's going to give you a diarrhea episode in 60% of the patients. You're pretty much guaranteed that if you're going to take these drugs, it's going to happen. So, you really have to prep the patient, and it works when you do.

Then understanding what you can do to mitigate that. It's one of the limitations, and it gets back to some of the earlier discussion we had during this which was, of course, the sequential application of these drugs, because when you do have GI upset and GI side effects, it's so common in so many of the immunosuppressives, that being able to do them one at a time, I think, is a real advantage to be able to successfully administer the drugs. And that's what lets us get at combination therapy. There was actually a study that took a look at the combination of the 2 antifibrotics together, and they published that you could successfully do it. But anybody who read the paper, or who's actually done it, knows better. What I mean by that is the rate of GI upset practically doubled because you gave 2 different mechanisms towards upsetting the GI tract.

In the setting of a clinical trial, manage to get the patient to buy in, you can get them to take both antifibrotics, but you can't get them to stay on 2. It just, it gets to be too much.

Blue Stop 9: Combination therapy

Dr. Volkmann: I think it's interesting, but the combination therapy, combining antifibrotic with immune suppressive, one thing I thought that was interesting from the SENSCIS trial where you had that subgroup of patients who were background mycophenolate plus nintedanib, when we looked at their side-effect profiles, they didn't have an increased risk of GI effects compared to those on nintedanib alone, or virtually mycophenolate alone, the ones who were on placebo. So, that motivated me to try the combination more in my practice, but I think the way you put it, that really you have to do this sequentially and mindfully, is important. If you start 2 new medications at one time, and the patient has a side effect, you don't know which one is the driver of that. So, if you start out and then, I usually wait a couple of weeks before I'd start the next one.

OPTIMIZING CLINICIAN-PATIENT COMMUNICATION AND PATIENT EDUCATION

Case #1: Pulmonary referral

Dr. Noth: As a pulmonologist, I really encounter the scleroderma-ILD cases in 2 ways. One, they come to me de novo, and basically, I end up referring them to a rheumatologist because I desperately want them involved. Or the rheumatologist sends them to me to get my opinion in regard to their lung involvement. Since what they're really looking for is the severity of the

lung function and whether or not antifibrotics would be appropriate, when to start them, and it really gets back to that earlier discussion you and I had about do you do them sequentially, do you do them concurrently, when would you start, how would you start, that kind of thing.

On the de novo ones, often it tends to be a little bit more subtle. I often tease there's a bit of a referral bias that happens. I have a tendency to check rheumatological labs, mostly because I'm a last resort, and I end up finding rheumatological labs as a result. And I've been teased over the years that we have no idea what the incidence and prevalence are in the population at large in regard to those antibodies, but I would argue that I'm seeing them underlying interstitial lung disease, and that it's probably appropriate.

It also helps me put them into the IPAF categorization, which is interstitial pneumonitis with autoimmune features. That's when they don't really meet ACR criteria, but every physician taking a look at them would say they have a sense that they might have some autoimmunity to them.

I'd like to start with a case. CG is a 44-year-old woman with a past medical history of asthma and hypothyroidism, PE, and anxiety. She was recently diagnosed with a connective tissue ILD and presented for a second opinion. She lived in an older house for a 10-year period that did have some mold and mildew. She had been having issues with a dry cough and throat irritation. That could be a combination, obviously, of allergies and bronchiectasis that we see in these patients. And a sense of dyspnea or shortness of breath for over a 3-year period. So, she's clearly symptomatic, and it had gotten progressively worse over time to where she was requiring some home oxygen. She denied any orthopnea or lower extremity edema or productive sputum. When we saw her in 2018, she had restricted pulmonary function tests. Her CT scan clearly had a ground-glass appearance, which would make me concerned for something like NSIP. Indeed, the physician had sent her for a VATS [Video-assisted thoracoscopic surgery] biopsy and gotten NSIP back. And we had gotten a positive ANA [antinuclear antibodies], and subsequently an SCL 70 that was positive. As a result, had started her on mycophenolate and prednisone.

Her past medical history and surgical history were very much what you'd expect. Some baseline anemia and anxiety and asthma, as I mentioned, but also underlying hypertension, some obesity-related obstructive sleep apnea, the history of PE we mentioned before; rare alcohol use. She had worked as a tax auditor. There was a parakeet, which always raises the concern of HP or hypersensitivity pneumonitis. Her surgical history was unremarkable, and there was a strong family history, with a mother with lupus, RA, and OSA [obstructive sleep apnea] as well.

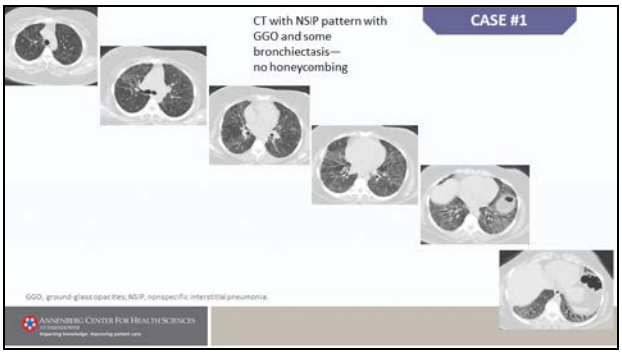
On physical, she didn't have vitals that day that we could see, but she was a pleasant, well-appearing African American woman. We know that we see a high predilection of some of these autoimmune diseases in African Americans. She was alert and oriented times 3, and well-nourished. She was able to speak in full sentences, without accessory muscle use or shortness of breath.

Her oropharynx was clear. There was nothing on her eye exam. Most importantly, we did hear minimal crackles at the lower lobes, and that helps support that there's an underlying interstitial disease that's not being appreciated. There was also clubbing present, and we often see that in these patients, particularly once they have an oxygen deficit. It seems to present in about 60% of the cases. The neurologic exam was unremarkable, and her skin was warm and dry. There were no mechanic's hands and no evidence of sclerodactyly.

Her ECHO showed a normal systolic function with a decent ejection fraction of 55%-60%. What was really interesting was the read on the CT scan.

Again, those areas of ground glass, slightly more pronounced at the lung bases, with some mild bronchiectasis in the lower lobes, more so on the right, with some slight reticulation and intralobular septal thickening in the right upper lobe. There was no significant air trapping, and that's important because it's one of the clues that we look for in regard to whether or not it's HP. There was no adenopathy appreciated. Now, that's also interesting because I can tell you that 75%-90% of the time there will be some adenopathy, and it really doesn't help to distinguish things very much. But overall, the CT pattern was consistent with a non-IPF diagnosis, and it was felt to be a possible NSIP, which we later discovered it was, but considerations for NSIP included hypersensitivity pneumonitis and the feeling was that this 2019 CT had progressed from 2016.

She'd had a bronchoscopy that was nondiagnostic and proceeded on to this VATS biopsy, which is important to note that it had a cellular phase of NSIP. So, we tend to divide, as pulmonologists, NSIP into 2 categories: the fibrotic vs NSIP. And this comes from a paper in the early '90s from *National Jewish*, which was Thomas King's group, at the time, that demonstrated that fibrotic NSIP behaved as badly as usual interstitial pneumonia, whereas cellular NSIP, where you saw inflammatory cells with less fibroblastic foci, seemed to respond to immunosuppression better. And this, of course, actually makes some sense.



What we have is a series of CT images demonstrating that ground-glass appearance that we showed in one of the other modules. Where you've got a few cystic changes that are really bronchiectasis cut on end, but overall, you get this hazy appearance.

Most importantly, and this is where the hints come into play, are these pulmonary function tests. So, the FVC is at 55% of predicted with an FEV1 [forced expiratory volume over 1 second] of 70%. That's going to be a high elastic recoil ratio. You're looking at a 90-plus ratio here. So, that's a fibrotic elastic lung, but the DLCO is 29%. Now, what I can tell you anecdotally is that the IPF cases have this pattern with a much lower DLCO. But the connective tissue disease patients do not. They tend to float pretty much in line with their FVCs. So, when you see a DLCO that is more dramatically reduced than the FVC, I'm looking for 1 of 2 things. Either I have an underlying UIP pattern that's not being appreciated and it's not truly a connective tissue disorder, or I've got a vascular insult, pulmonary embolism, pulmonary hypertension, something that's lowering that DLCO, I won't say independently, but not directly related to the fibrotic process itself.

This case really addresses a lot of different issues, right? We've got an Scl-70 [antibody] positive patient, so we would expect an NSIP pattern without pulmonary hypertension, but I will raise everybody's memory that, in the history, she had a history of PEs. So, she could have chronic thromboembolic disease as a mechanism for pulmonary hypertension independent from the seropositivity pattern that we would expect. She had a typical NSIP pattern. Did she really need a VATS? Probably not. Truth be told, that CT was more than good enough to tell you that it was not going to be a UIP pattern. One could make an argument, if you didn't know it was scleroderma, that you'd want that biopsy to make sure you weren't missing something, but otherwise I think in context it was enough.

I think the bigger issue is addressing her comorbidities, right? She's already treated with mycophenolate and prednisone. So, the questions that arise are what is the prognosis, what are the factors involved, and what are the other treatment options? Would you add nintedanib at this juncture? I'm going to open it to my colleague a little bit and see what she thinks about that.

Dr. Volkmann: I think it's a great question. Clearly, this patient had progression of her lung disease, which you mentioned on her CT despite treatment with mycophenolate. So, this would be a case where you maybe would consider changing her mycophenolate or adding something to it. Usually, how I make that decision is I also look to see what other parts of the scleroderma responded to the mycophenolate. So, if, for example, this patient had skin disease that improved on mycophenolate, I will probably keep them on the mycophenolate and add something like nintedanib to it. But if the patient didn't derive any benefit from the mycophenolate for any aspect of the scleroderma, even outside of the lung, then I will probably stop it, and then, at that point, switch it to something else, like nintedanib or rituximab or tocilizumab.

Dr. Noth: This is where, again, having multiple specialties at play, my repertoire stops at that cell set. So, I don't know that I would have been comfortable to switch. I certainly have used rituximab in other connective tissue disorders, but I don't know that I would have been comfortable here just from lack of experience.

We started to work her up for pulmonary hypertension, looking for chronic thromboembolic disease. We made sure, you made this point earlier, treating the allergic rhinitis with fluticasone to make sure that she can breathe as easy as possible. She gained weight. If we want to improve a patient's shortness of breath, believe me, weight loss does matter. It is not a linear relationship; it's an asymptomatic, asymptotic relationship. And so, very small weight gains will translate into very big sensations. And then, of course, starting the nintedanib on top, and that script was being filled by rheumatology.

The recommendations were to continue the mycophenolate as prescribed. We took a look at the BNP [brain natriuretic peptide] and the TTE [transthoracic echocardiogram] with a bubble study, which proved to be negative. Because of the prednisone, we did add sulfamethoxazole/trimethoprim to ensure the PCP [*Pneumocystis carinii* pneumonia] prophylaxis was kept in check. And then, of course, making sure that the vaccinations were up to date. And what's missing on this slide is, in today's era, of course we would add the COVID vaccine to that list, as well. And then regular monitoring on a 3-month basis.

Incorporating Patient Engagement

Dr. Noth: We have to engage in optimization of the education of the patient. All of this doesn't work if we don't get patient buy-in. The drugs are a task, as are these comorbidities, and so we have to get the patients to understand what those comorbidities mean in terms of their overall disease course and their overall sense of well-being and educate them on the pros and cons of that immunomodulatory therapy. In the case of the antifibrotics, it's really about expectations in regard to the side effect profile, because most of it is pretty tolerable, but they need to know upfront what they might be experiencing and how to handle it. So, really an open discussion over what the remainder of the work-up would look like, and the monitoring of the patient, as well as encouraging to ask questions and provide feedback in the journey of their care. And then, obviously, that co-management with rheumatology so they hear a consistent message across the board over how we handle this.

Lastly, empowering them. They've got to be empowered with medical decision making. You know, I always tease, I have a critical care doc at heart from a first training, and in the intensive care

unit, it's a very paternal exercise. We make all the decisions. You don't really, and the patient doesn't really, want to be engaged at that juncture. They just want to know how you're going to fix them. But when you're talking about treating chronic illnesses, it's a different story. You've got to get the buy-in, and the buy-in comes from shared medical decision making. That means teaching the patients with regard to the side effects: GI upset, signs and symptoms of pulmonary hypertension and oxygen therapy, as appropriate. I always tease, it's actually the cheapest medication we've got with the highest efficacy in terms of prolonging their lives.

Dr. Volkmann: I think [what] you brought up about empowering and patients is so important, and partly because patients' adherence to medication probably largely depends on their understanding of why they're taking the medication, because sometimes they may not necessarily feel better like you would if you took a pain reliever, you'd immediately feel better. These medications don't necessarily make someone instantly feel better. It's a long-term process, and so I find that the education part of this is really important for patient adherence. I think it also gives them, too, a better sense of control of their own destiny. I think when a patient is diagnosed with one of these very difficult autoimmune diseases, it can feel like everything in their body is out of control, and if you start to teach them about their illness and teach them about why we're using these medications, they regain some of that control, and I think that can improve their quality of life too.

CASE #2: SUSPECTED ILD IN ELDERLY PATIENT

Dr. Noth: We have a 78-year-old woman with a past medical history of hypertension, liver disease, paroxysmal afib, on anticoagulation, who had a suspected interstitial lung disease and was establishing care in the interstitial lung disease clinic. She had presented with symptoms occurring about a year ago, in March of 2020, when she presented with some chest pain, and she saw her primary care who referred her on to a pulmonologist. She endorsed a dry cough, which is the number-one symptom they present with, even I think before shortness of breath. She stated that cough had significantly improved since her birds were removed. That's always a huge tell-tale. In the past, she had had other pets in addition to birds, which included dogs, cats, gerbils and rabbits and a snake, as a child. She walks at least 1 mile and swims daily. So, she's got quite a bit of exercise tolerance.

She had never smoked, never vaped, nor lived with any smokers, and no family history of an autoimmune disease. Her daughter had some asthma. Didn't grow up on a farm; no other real exposures to speak of. Fun tidbits, she had lived in Norway; she had spent a semester at sea; she had visited the Amazon rainforest, but most of her life had been spent in the Charlottesville area working as a physical therapist.

The important part of her past medical history here is really the afib, with some DJD [degenerative joint disease], some dyslipidemia; a question of interstitial lung disease; mother died of leukemia; father had Alzheimer's. Hobbies included stained glass, but that was 30-40 years ago, and she had had 2 birds, which have since been removed, and the travel history that we've highlighted.

On her physical, the most important thing is the absence of crackles, in this case. So, if there are not crackles, I will tell you it is not IPF. I think that's at 100%. It has basically got to be there. Now, that doesn't mean there isn't an interstitial lung disease, but you can certainly take a lot of the UIP pattern off the table. And so it does leave you wondering about airway-centric processes.

Her laboratories: she demonstrated an Scl-100, and I put a little note in here that there are more than just the Scl-70 cases, right, and I think this is important to recognize. And her HP panel was positive for birds, parrots, and parakeets. Now, it's important to recognize that's very helpful in the proper setting, but way more people will come up

positive for these tests than actually have HP. It's helpful, definitively, if it's negative; it's helpful if it's positive in the right setting; but positive on its own is probably not enough information.

Then we had the CT scan from May of 2020 where she had intralobular septal thickening symmetrically, involving both lungs with a mild basilar predominance, no honeycombing or air trapping, and it was indeterminate. Now, indeterminate is what the radiologist says when they throw their hands up. So, what it means is it's just not in any of the groups that they care to put a bucket together, and it's basically completely…, it's not nonspecific interstitial pneumonitis; it's nonspecific. Basically, unclassified. And there was enlargement of the main pulmonary artery, as may be seen with pulmonary hypertension. And so she had a TTE, which showed normal LV [left ventricle], and normal wall thickness, and an ejection fraction that was also normal.

When you look at her pulmonary function tests, they were very telling in that they're mostly normal with an FVC of 83% and an FEV1 of 87%. But the subtlety is that there probably is a little something in that the elastic recoil measure, which is the ratio of those 2, that is probably a little elevated. The DLCO is also very mildly reduced at under 75%. But when you look at the 6-minute walk, you've got complete preservation of oxygen saturation, and 332 m is pretty good. So, whatever is going on, it's not clinically important, just yet.

My initial assessment was we thought this was HP. But the CT scan didn't have any air trapping. So, with the Scl-100 being positive, now wondering whether or not it's really that subset of scleroderma patient. We published a paper a couple of years ago that demonstrated what we called HPAF as opposed to IPAF, which was basically hypersensitive pneumonitis with autoimmune features, recognizing that we see a higher rate of the interaction of the 2.[42] We're wondering if we're simply seeing that as a very early effect. But, at the end of the day, we're not treating, and we're not treating at this juncture because she's very much in normal range.

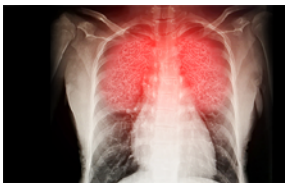
The Power of Patient Engagement

Dr. Noth: I think that much like the previous case, communication with the patient is everything. Discussing the possibilities over what that scleroderma pattern may mean. Even if it is scleroderma, whether or not there's a concern. Even if it's HP with the scleroderma, is that a concern given her current level? And then discussing what the options are, depending on how they feel about it. I think, again, age would come into effect. This was a 78-year-old, so the notion of starting an immunomodulatory therapy and immunosuppressive therapy is less enticing in a 78-year-old than it is in a 48-year-old. It's not that I'm not open to it. It's something I think has to be had in an open discussion with the patient, and whether or not to add an antifibrotics or not, I think becomes a discussion.

It really brings back that shared decision-making issue, and one getting a rheumatologist to weigh in on what they thought the meaning of that Scl-100 is, I think would be extremely valuable.

Dr. Volkmann: I like the point you made, too, that sometimes these conditions are not mutually exclusive. So, we can have patients who have connective disease, related ILD, they have underlying scleroderma, but then their CT has features of HP, and they have an exposure history, and oftentimes we diagnose them with both. And we treat it, sometimes very similarly as well, but I think it's important that we consider these other diagnoses, because we can educate the patients about removing their exposures where possible. That might help improve their outcomes too.

Dr. Noth: Again, it's really about empowering the patient. It's making… when they understand what's going on, they make better decisions, and they can make the right decisions for themselves.



SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE:
MAKING CONNECTIONS, ELEVATING CARE

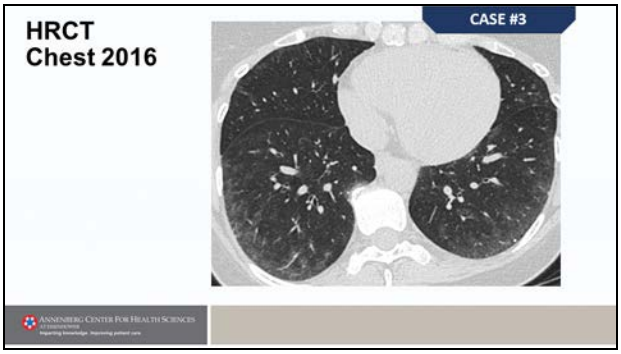
Case #3: Rheumatology presentation

Dr. Volkmann: This is a 47-year-old, Hispanic female, who in 2011 developed Raynaud's phenomenon, and then, 2 years later, developed puffy hands and was found to have a positive ANA [antinuclear antibodies]. The patient saw an outside rheumatologist, and was diagnosed with rheumatoid arthritis, and was started on methotrexate. I would say that this is a common misdiagnosis. Early in the course of scleroderma when patients just have puffy fingers, they're usually either diagnosed with rheumatoid arthritis or lupus. But then, a year later, she developed a dry cough, and her primary care doctor thought it might be due to GERD. Then, a year after that, she starts to develop fatigue and dyspnea after exercise, but she thinks, maybe I'm just out of shape.

Finally, in 2016, she just doesn't feel like she's doing any better on the methotrexate, so she decides to get a second opinion, and she comes to see us in 2016 and, on exam, she has bibasilar crackles. She has sclerodactyly, which basically means skin thickening of the fingers. Her modified Rodnan skin score (mRSS) is 2, and this is the way we assess the extent of skin involvement. We look at 17 different parts of the body, and we rate them from 0 to 3, with 0 being no skin involvement from scleroderma, and 3 being maximum skin involvement. So, it's somewhat of a subjective assessment tool, but it works well if it's done by the same assessor every time. This patient had a very low mRSS, only 2, because she just got 1 point for each set of fingers. And she did have positive nailfold capillary changes that we talked about before.

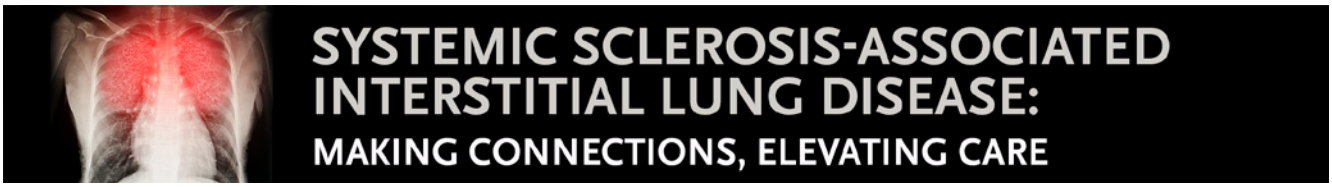
On her labs, she had a normal CBC and comprehensive metabolic panel. She did have elevated inflammatory markers, a normal CK [creatine kinase], and aldolase. Her serological profile was notable for a positive ANA and a positive PM-Scl antibody.

For her initial assessment, we diagnosed her with limited systemic sclerosis, and we also got pulmonary function testing, and she was found to have restrictive physiology. She had a decrease in her FVC, it was 72% predicted; a decrease in her DLCO, it was 57% predicted. We also got an echocardiogram, and she had a normal ejection fraction. Her RVSP [right ventricular systolic pressure] was estimated between 26 and 31. Her peak velocity of TR [tricuspid regurgitation] was 2.57, and then we also assessed her esophagus. At that time, she had a small hiatal hernia, which is not uncommon in scleroderma, as well as absent contractility.

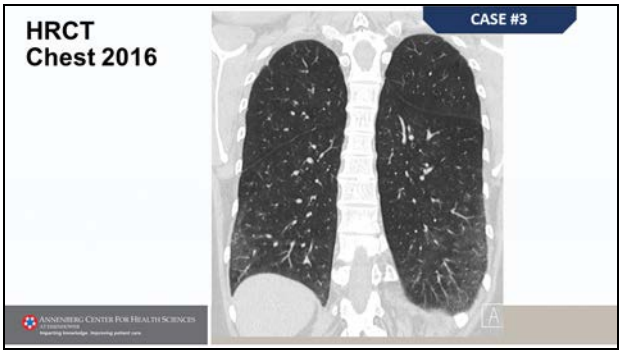


I'd like to move on to the CT of the chest, and I'd love to hear your assessment of this, Dr. Noth. What do you see when you look at this CT that she had early in the course of her lung disease?

Dr. Noth: It's a great representation, right, of the ground-glass appearance; very soft presentation, almost looks a little tissue-paperish, right? You can really see that gentle haze, and it's one of the reasons that it becomes so critical that we do the prone and supine, because you want to see how much of that were to clear, particularly if she were obese, as an example, because you get microatelectasis. I will say this one really does appear more like an NSIP-type pattern as opposed to just clearing from atelectasis, but it's just to give you the comparison on the contrast.

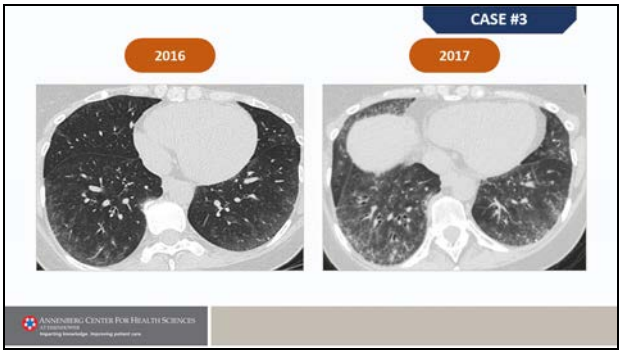


Dr. Volkmann: I think one of the things that comes up sometimes, when let's say a rheumatologist is ordering one of these CT scans, if they don't specify I'm looking for ILD, sometimes a radiologist—particularly one that maybe isn't a thoracic radiologist—might interpret that as atelectasis. And so, I think specifying what you're looking for sometimes can help in these early processes. I don't know if you agree with that?

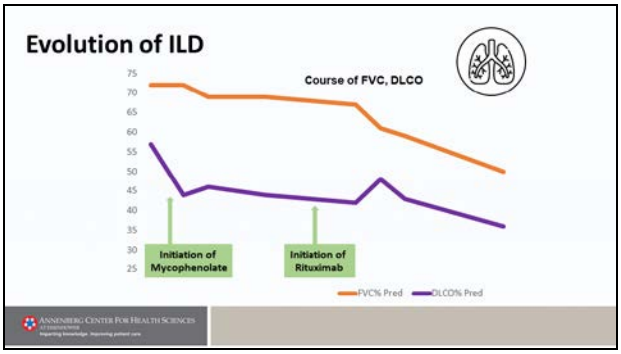


Dr. Noth: Absolutely. No, listen, small social point, I suppose, thoracic radiology is one of the specialties that's been shrinking, and more and more general radiologists are reading thoracic CTs, and the comfort zone for this type of material is limited, even in thoracic radiology. And so the level of expertise is limited, as well, so bringing it to their attention becomes very important.

Dr. Volkmann: Right. So, then over the course of the next year, she developed inflammatory myositis as well as worsening dyspnea on exertion. And then we got another CT, and over the course of this time, the patient had been treated.

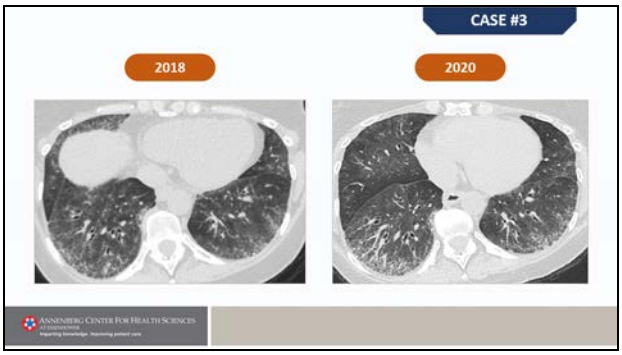


I just want to show the evolution here. And often, when we're in our multidisciplinary discussion group, we like to look at these serial CT scan, as well as serial PFTs, but I think this slide nicely demonstrates a clear case of progression of interstitial lung disease that, again, is quite obvious, even to the rheumatologist.



If we look at her evolution in terms of her pulmonary function testing, this patient was started on mycophenolate when she started to have a decline in her PFTs and her symptoms, and that stabilized things for some amount of time, but then she continued to have decline. She also developed this myositis, so that's why rituximab was added for this patient. You know, unfortunately though, this was a patient again with this PM ScL-70 antibody, which is associated with a more progressive phenotype.

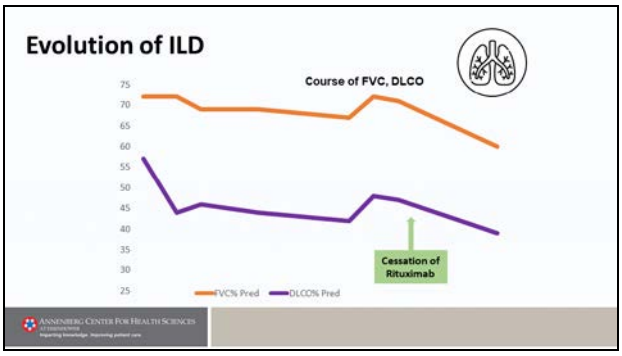
Again, rituximab led to improvement of her myositis, but this was all, of course, going on during the pandemic. All of us, as clinicians, have faced a lot of challenges when it comes to therapy adherence during this time, and for obvious reasons, patients have a lot of concerns about being on immunosuppression and the risk of COVID. So, this patient stopped her rituximab in early 2020, and basically, following cessation of all therapy, her ILD unfortunately got worse.



What do you think when you look at these scans, looking back from 2018 to later in 2020?

Dr. Noth: I'm just really struck by how much more fibrotic it appears than ground glass now, right? Much clearer, less fuzzy image that speaks to the reticular fibrosis that happens.

Dr. Volkmann: Right, exactly, and this really mirrored what we saw in terms of her pulmonary function where, when she did stop the rituximab, there was again a further decline in the FVC and the DLCO.



Our next steps for her, she did get vaccinated in the spring of 2021, and then, shortly thereafter, resumed rituximab. Then we decided to be aggressive and add on antifibrotic therapy, since, as you mentioned, her CT features were more fibrotic at that point anyway, and it was to see if the combination would lead to a better improvement.

With some case reflections that I think are important to mention here, and not as to really consider early intervention when risk factors are present. So, we talked about things like male sex, African American race, increased age, the disease-related features—so more diffuse skin disease, higher skin score at baseline, and the shorter disease duration, and really this is because this is when the ILD is most likely to progress.

The other thing I'll mention about the PFTs that I think is interesting is that sometimes it's not just the baseline PFT that's important, but it's how the PFTs evolve in that first couple of years. We looked at patients who participated in the Scleroderma Lung Studies I and II, and then we looked at their long-term survival. We had up to 12 years of follow-up for Scleroderma Lung Study I, and up to 8 years in Scleroderma Lung Study II, and we found that the trajectory of the FVC over that first 2 years of the study was actually a more important predictor of long-term mortality than their starting off FVC. So, don't let the normal FVC at baseline mislead you, because if it declines rapidly in that first year, that can be really problematic.

Dr. Noth: I think that's a hugely important point I've been touting for years. It's not where you are, it's how fast you got there. Right?

Dr. Volkmann: I'm sure in patients that you see with IPF, this is a big issue.

Dr. Noth: It's everything, right, because we'll see them, and we just don't know when it started. We don't have a start date for these processes. So, I often tell a patient who may have moderate disease, that they may have a very long time to live, whereas somebody who has a more rapid decline over a short period of time, but good PFTs, might be in a whole lot more trouble.

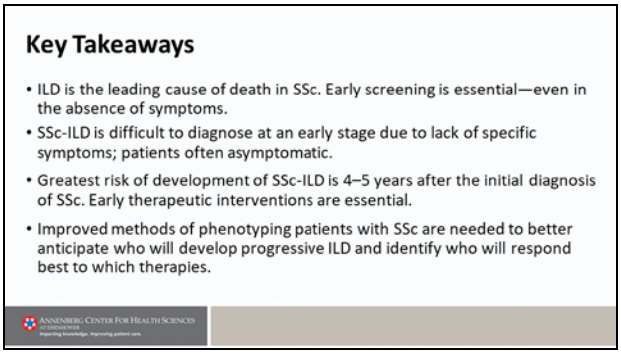
Dr. Volkmann: When we think back to her original CT scan, she didn't have a great extent of reticulation at the time of her ILD, but she had

some of these risk factors for progression, including that PM-Scl antibody, and she had elevated inflammatory markers, the CRP. If we measured her KL-6 and CCL-18, they might have been elevated, as well.

I think we have just tried to talk a lot about how important it is to communicate with patients and inform them and their caregivers about the importance of treating these conditions early on, because, again, we're really trying to prevent the loss of lung function. I try to encourage all my patients to ask questions, and I do this in a way where I don't just say, do you have any questions, because sometimes that really puts a patient on the spot. I'll often end an encounter by saying, "What questions do you have for me?" Then I'll tell them, if you don't have any questions right now, when you go home and you talk to your family or you talk to your friends, if you have questions then, write me a message, because sometimes it's hard to think of them on the spot, especially if you're getting a new diagnosis or new treatment plan. But I think that the dialogue we have with patients really continues even after the encounter.

Dr. Noth: I think that's a hugely important point. I tease, dealing with IPF far more than scleroderma, it tends to be a little like a cancer diagnosis. They don't hear anything after that. So, there's a lot of deafness that goes on for a stretch, and then they get home, and they start to think about things, and some of the visit then comes back to them, and so we do the same. We encourage them to write down their notes and questions, and call us, email us, do whatever's necessary to get those questions answered, because it is a process in educating them.

Dr. Volkmann: I find too that, in addition to the medications, there's other things we can recommend. I find, for example, pulmonary rehabilitation to often be very helpful for patients. I think this is part of the empowering process if they learn about exercises and aerobic activity that they can do safely with supervision, then it inspires them to continue this at home and stay active and not become too reconditioned.



Without a doubt, ILD is the leading cause of death in scleroderma. This is why we spent the last couple of hours going through these in these various modules, because it is so important to pick up on. And early screening is really essential if we're going to make a dent in preserving lung function in these patients. Even in the absence of symptoms, we know the rate is so high for an underlying interstitial lung disease in scleroderma, even when not clinically obvious when we start with the patient, but it might progress down the road. And so, at the very least, being able to monitor them to figure that out becomes critical. And so, diagnosing at an early stage with the lack of specific symptoms is really a part of the task, and I've been trying to get my rheumatology colleagues—and they really have picked up in that regard—into screening with pulmonary function tests as a means of ensuring that they keep an eye on these patients.

Dr. Noth: Absolutely. And I feel like the future of this field is hopefully being able to apply more of a precision-medicine approach to how we treat these patients. We have now at our disposal a number of different therapeutic options that target different pathways in the immune system, and my hope is that we'll be able to discover biomarkers that will help predict whether someone will preferentially respond to an antifibrotic or an

immune suppressant. But, at the very least, I think we can improve our ability to identify these patients who are more likely to progress, early on, and these are the patients we really want to treat aggressively.

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