IAN ODELL: Scleroderma is a rare autoimmune disease. It affects about 240 people per million. And going on, I'll discuss both the clinical and scientific aspects of the disease. And so we'll start with clinically-- so it's most notable in the skin, as the name implies, and it can have a wide range of severity.

And so what happens is a patient will notice-- or they may notice puffiness of their hands and face initially. Clinically, this is typically a non-pitting edema. And this puffiness can last for about 6 to 12 months. Now, in certain cases, it may last shorter, and the disease may progress more rapidly.

After this puffiness resolves, then the next phase is a sclerotic phase in which thickening and induration of the skin occurs primarily in the same locations on the hands and face. Now, it may just stop there depending on the patient, but the thickening and induration may also extend more proximally past the elbow and all, and may affect even all of the skin of the body.

And these locations, whether it's proximal or distal to the elbow and knees, really define two separate subsets. One is considered to be localized systemic sclerosis or scleroderma, and the latter is diffuse systemic sclerosis. And so the degree of skin that's affected in the disease also correlates with the probability and extent of how much it might affect the internal organs.

And the most problematic organ, if involved, are the lungs. And this is the highest cause of death in patients with scleroderma. Now, there are two types of lung disease that could occur-- interstitial lung disease, in which we get fibrosis of the lung tissue, and a second called pulmonary arterial hypertension as well. And there are therapies that target more of the pulmonary arterial hypertension than the interstitial lung disease.

So in addition to the lungs, scleroderma can also affect the kidneys. And this used to be the most common cause of death in these patients-- from scleroderma renal crisis. However, with the use of ACE inhibitors to control the hypertension, patients have had longer survival.

In addition to the lungs and kidneys, scleroderma can rarely affect the heart, and actually pretty commonly affect the gastrointestinal tract. In particular, it's noted by difficulty swallowing in a subset of a type of patients called CREST syndrome.

And so the reason for this wide range of phenotypes is not understood. But one core underlying phenotype that happens in greater than 90% of patients with scleroderma is that they have Raynaud's phenomenon. And what this is a reactive process to cold, to exposure to cold, in which the patients get a vasospasm, in particular, on their hands, and it can be very painful.

Raynaud's in itself is very common in the general population, but it's just much higher in patients with scleroderma. And a number of patients that I see actually have Raynaud's as their presenting issue-- that they note-- but this even precedes that puffiness and edema of the hands and face.

And so it leads into how is this happening? So one aspect is the vascular aspect of it. That the Raynaud's-- they have this increased susceptibility of vasospasm, and a number of patients get telangiectasias on their face, in their mouth, as well as on their hands. And these are a specific type of telangiectasias called mat telangiectasias.

So there's two lines of evidence suggesting they're at least a vascular component to it. But the leading theory within the scientific community is that it's an immune-mediated process. The strong evidence for this is that we do see some improvement with immunosuppressive medications.

And then also, similar to scleroderma, there's another disease-- that's sclerotic graft-versus-host disease, which occurs after stem cell transplant. And while not identical, this can mimic scleroderma both clinically and histologically.

And so if we look into the immune populations that occur in scleroderma, there's a long history and it's not entirely clear exactly what's driving disease. Decades ago, they saw an increase in mast cell numbers in the skin of patients with scleroderma. And they thought that this might relate to that puffiness that we see initially. However, further studies didn't find any conclusive evidence for mast cells driving disease.

Then later on, they looked mainly at T cells and B cells and different subsets of T cells and B cells. T cells in particular, there's a subset of T regulatory cells which play a role in wound healing. And so the thought was perhaps it's an over-activation of this wound-healing response-- in increased T regs.

There's not great evidence for B cells, although we do know that patients with scleroderma develop autoantibodies. In particular, there's clinically used clon-- autoantibodies, such as Scl-70, anti-centromere, and anti-RNA pol III. So while these are great clinical markers, they themselves aren't necessarily what's driving disease.

And also, more recently, they found autoantibodies against PDGFR beta, or against PDGFR, and these antibodies are actually activating the receptor. And so it's thought-- at least in a subset of patients-- that this activation of PDGFR by an autoantibody leads to the disease. And indeed, further trials with imatinib to inhibit this process seemed initially to help a few patients, but hasn't really panned out in larger studies with more patients.

And now more recently, there are different subsets of myeloid antigen presenting cells, such as monocytes and plasmacytoid dendritic cells, which have really had the strongest evidence towards playing a causal role in the disease.

So in particular for monocytes, there's a subtype of monocytes termed SatM. And what they found is in mice if you deplete this subset of monocytes, then these mice are protected from developing fibrosis in different models of fibrosis.

And second, the plasmacytoid dendritic cells-- so this is a subset of conventional dendritic cells-- and these produced the largest amount of Type 1 interferon. And Type 1 interferon-- it's a cytokine that is increased in both scleroderma and lupus. And it's not clear exactly why-- if this cytokine is driving disease, but at least-- and it's found to be increased in patients. And if you deplete the plasmacytoid dendritic cells, the mice that have this depletion are also protected from developing fibrosis.