Saturday, May 29, 2021
11:00am–1:00pm EDT

CANADIAN Scleroderma Summit

Pre-Meeting Executive Summary

DERM.CITY/SCLERODERMA

CHRONICLE ACADEMY

Mallinckrodt Pharmaceuticals

What is Scleroderma?

Scleroderma is a group of rare but chronic diseases that involve the hardening and tightening of skin and connective tissues due to the over-production of collagen. It is generally thought to be an autoimmune disease, and, according to the American College of Rheumatology, affects about 75,000 to 100,000 people in the U.S.; the majority of those are women between the ages of 30 and 50. In Canada, up to 40,000 people may be living with scleroderma.

There are two types of scleroderma: localized and systemic. Localized scleroderma can take the form of either morphea or linear scleroderma. Systemic scleroderma can be either limited, diffuse or sine.

Localized scleroderma affects the skin, but not the internal organs. Morphea, the most common form of localized scleroderma, is characterized by oval patches of inflamed, and often discoloured, skin on the trunk, face or extremities. In linear scleroderma, bands of skin will harden or thicken on the trunk, the extremities or both.

Systemic scleroderma also affects the internal organs, especially those of the digestive, circulatory, pulmonary and muscular systems.

Limited scleroderma is often referred to as CREST, for the symptoms these patients may display:

- Calcinosis (small white lumps of subcutaneous calcium)
- Raynaud's Syndrome (poor circulation in the extremities due to narrowing of blood vessels and a decrease in blood flow—fingers often turn white or blue, and patients can be very sensitive to cold)
- Esophageal dysfunction (patients can have difficulty swallowing, heartburn or regurgitation)
- Sclerodactyly (the skin of the fingers, and perhaps toes, becomes thick and shiny, and can make digits difficult to move–digits may become fixed in a bent position)
- Telangiectasi (small clusters of blood vessels in the skin become dilated, particularly on the face, fingers and palms of the hand)

Limited scleroderma generally manifests over an extended period of time, often 10 to 20 years. It affects the skin first, before symptoms affect internal organs.

Diffuse scleroderma affects more of the skin and more internal organs. It can manifest on the face, neck, torso, hands, arms, feet and legs. Internally, it can involve the esophagus, the digestive tract, kidney, heart and lungs, leading to a fibrous hardening, or sclerosis, of those organs. In the kidneys, this can lead to high blood pressure and, ultimately, kidney failure. In the lungs, scleroderma can lead to scarring, pulmonary hypertension and breathlessness. In the heart, it can lead to scarring of the heart muscles, chest pain and irregular heartbeat.

Sine scleroderma can display the symptoms of both limited and diffuse scleroderma. Unlike other forms of the disease, though, sine scleroderma does not generally involve the skin.

As well as the symptoms already discussed, scleroderma can also lead to muscle weakness and pain; joint stiffness and soreness similar to that found in arthritis; Sjogren's Syndrome which manifests as dry eyes and mouth from a decrease in secretions from tear ducts and salivary glands; and dental problems from the tightening of facial skin and tooth decay from dry mouth, which can lead to problems with swallowing.

Causes of Scleroderma

There is no definite cause of scleroderma. Studies suggest it may be caused by any or all of immune system problems, genetics and environmental triggers.

Immune system problems: Scleroderma is usually thought to be an autoimmune disease, and 15 to 20% of those with scleroderma also have another autoimmune disease, often including rheumatoid arthritis, lupus or Sjogren's syndrome.

Genetics: While scleroderma is thought to be neither contagious or inherited, in rare cases the disease does appear to run in certain families with particular gene variations. Choctaw Native Americans also appear more susceptible to scleroderma. Females comprise about 80% of those with the disease. A recent study* on juvenile localized scleroderma showed that the activity of 589 genes was significantly different between children with juvenile localized scleroderma and healthy children. Seventy-five per cent of those genes were less active among patients, while 25% were more active.

Environmental triggers: Some studies suggest that exposure to certain viruses, medications or drugs, or repeated exposure to certain harmful substances or chemicals, may increase the risk of scleroderma.

* Schutt, C., Mirizio, E., Salgado, C., Reyes-Mugica, M., Wang, X., Chen, W., Grunwaldt, L., Schollaert, K. L. & Torok, K. S. (2021), **Transcriptomic evaluation of pediatric localized scleroderma skin with histological and clinical correlation**. Arthritis & Rheumatology. https://doi.org/10.1002/art.41758

Treatment

There is currently no one treatment for scleroderma. Physicians often prescribe medications to treat the symptoms, including steroids to reduce swelling and pain; blood pressure medications that can also help treat Raynaud's; immunosuppressant drugs; medications for heartburn and indigestion; antibiotics and pain relief medication.

Recent Studies

A number of studies have suggested that the use of extracorporeal photopheresis (ECP) may be beneficial to patients with scleroderma. ECP is a cell-based immunomodulatory treatment that involves drawing blood from the patient, separating the leukocytes from peripheral blood, exposing them to a photosensitizing agent and then to ultraviolet A light, and then reinfusing them back into the patient.

A 2005 study†, which compared the efficacy of ECP to placebo, concluded that while more robust research is needed, "Photopheresis induced significant improvement of skin and joint involvement in patients with scleroderma of recent onset."

† Knobler, R. M., French, L. E., Kim, Y., Bisaccia, E., Graninger, W., Nahavandi, H., Strobl, F. J., Keystone, E., Mehlmauer, M., Rook, A. H., Braverman, I., & Systemic Sclerosis Study Group (2006). **A randomized, double-blind, placebo-controlled trial of photopheresis in systemic sclerosis**. Journal of the American Academy of Dermatology, 54(5), 793–799. https://doi.org/10.1016/j.jaad.2005.11.1091

Recent Studies (cont'd)

A 2020 study‡ reviewing the existing literature on ECP concluded, "multiple lines of evidence suggest that ECP may be a safe and possibly effective therapy for patients with scleroderma, specifically demonstrating improvement in patients with cutaneous manifestations of the disease." An ongoing German case study, slated to conclude in February 2022, is investigating the effects of ECP on 10 participants.

Researchers at the University of Michigan have recently developed an algorithm, called DETECT, that allows physicians to spot pulmonary arterial hypertension in patients with scleroderma.§ It's recommended that patients with scleroderma receive an annual echocardiogram, but those studies often fail to predict hypertension in the early stages of scleroderma or in those who are asymptomatic.

"These ultrasounds miss around one in three patients who may have pulmonary arterial hypertension," said Dinesh Khanna, senior author of the study. "And by the time we diagnose a patient so late, the story is over—the patient will likely die in the next two or three years."

‡ Du, A. X., Osman, M., Gniadecki, R. (2020). **Use of Extracorporeal Photopheresis in Scleroderma: A Review**. Dermatology 236, 105–110. https://doi.org/10.1159/000501591

§ Young, A., Moles V. M., Jaafar, S., Visovatti, S., Huang, S., Vummidi, D., Nagaraja, V., McLaughlin, V. & Khanna, D.(2021). **Performance of the DETECT Algorithm for Pulmonary Hypertension Screening in a Systemic Sclerosis Cohort**. Arthritis & Rheumatology. https://doi.org/10.1002/art.41732

Scleroderma Summit 2021 Agenda – May 29

Opening Remarks – What is Scleroderma?	Dr. Shafiq Qaadri
Keynote: Therapeutic Options for Scleroderma in 2021	Dr. Janet Pope
Canada's Rare Disease Drug Strategy	Durhane Wong-Rieger
Access to Treatment: Industry Perspective	Lorraine Boyle
Access to Treatment: Patient Perspective	Maureen Sauvé
Scleroderma or Not? Skin Clues for Early Diagnosis	Dr. Robert Gniadecki
Current Research in Scleroderma	To Be Announced
Putting Patients in Touch with Support	John Malcolmson
Closing Remarks – Conference Summary	Dr. Shafiq Qaadri

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This executive summary was prepared as background reading for delegates to the 2021 Canadian Scleroderma Summit.

555 Burnhamthorpe Road, Suite 306
Toronto, ON M9C 2Y3

Phone: +1 (416) 916-2476
Fax: (416) 352-6199
Email: health@chronicle.org

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