SKIN PATHOLOGY ARTICLE

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Information for Doctors

A rare connective tissue disease – scleromyxedema

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Case study

An 80-year-old female presented with a 6-week history of progressive bilateral hand swelling, pain and the development of multiple nodules. Her past medical history includes hypertension and coronary artery disease. A broad workup including a full connective tissue screen, ultrasound and echocardiogram did not reveal any abnormalities. X-ray of the fingers showed no chondrocalcinosis. She has no known renal or thyroid conditions. There was no response to 50mg oral prednisolone and intra-articular steroid injection.

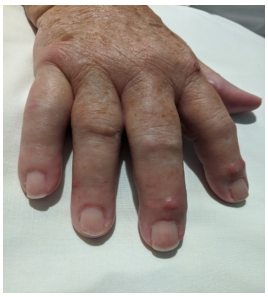

Figure 1. A clinical picture of the patient showing multiple nodules on the hands

A skin biopsy was taken for histological examination.
The microscopic examination revealed an increase in cellularity of the dermis with fibroblasts. There was a focal increase in stromal mucin on an alcian blue stain. There was also patchy dermal fibrosis. Some fragmentation of elastic fibres were noted. No granulomata, necrosis or vasculitis are seen.

After taking into consideration the clinical findings, a diagnosis of scleromyxedema was rendered. The patient was subsequently admitted to the hospital for further investigations and management. A repeated skin biopsy showed similar features. No gammopathy was identified. The patient was treated with intravenous Immunoglobulin therapy.

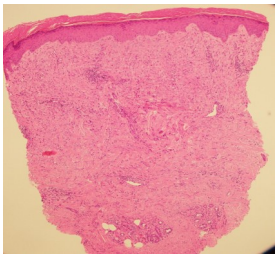

Figure 2. A microscopic picture at 2X

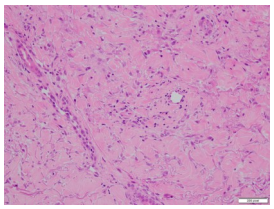

Figure 3. Dermal infiltrate of fibroblasts and fibrosis (20X)

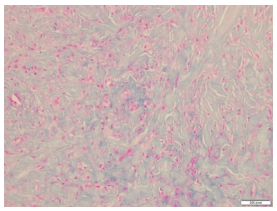

Figure 4. Alcian Blue stain highlights the background mucin (20X)

Scleromyxedema, also known as diffuse/generalized and sclerodermoid lichen myxedematosus or Arndt-Gottron disease, is a rare primary cutaneous mucinosis characterized by a generalized, papular and sclerodermoid, cutaneous eruption that usually occurs in association with monoclonal gammopathy. It typically affects middle-aged adults between the ages of 30 and 80 years with no race or sex predominance.

Rongioletti and Rebora defined scleromyxedema by the following criteria: (a) generalized papular and sclerodermoid skin eruptions; (b) mucin deposition, fibroblast proliferation, and fibrosis on histology; (c) the presence of monoclonal gammopathies; and (d) the absence of thyroid disorders. The pathogenesis is unknown. It is hypothesized that circulating cytokines, such as interleukin (IL) 1, tumor necrosis factor (TNF)-alpha, and transforming growth factor (TGF)-beta, are known to stimulate glycosaminoglycan synthesis and fibroblast proliferation in the skin, could play a role.

Clinically, the cutaneous manifestations include a widespread eruption of 2 to 3 mm, firm, waxy, closely spaced, dome-shaped or flat-topped papules involving the hands, forearms, head, neck, upper trunk, and thighs. Papules are often arranged in a linear fashion, and the surrounding skin is shiny and indurate (ie, sclerodermoid) in appearance. The glabella is typically involved with deep, longitudinal furrows that produce the characteristic leonine face. Deep furrowing also is typically evident on the trunk or limbs associated with redundant skin folds (known as the "Shar-Pei sign"). Patients with scleromyxedema can have a number of extracutaneous internal manifestations, including neurologic, rheumatologic, cardiovascular, gastrointestinal, pulmonary, and renal manifestations of the disease. It is usually associated with monoclonal gammopathy. The monoclonal protein is most commonly igG-Lambda.

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However, less frequently, a different monoclonal protein type is present. Cutaneous and extracutaneous involvement can lead to significant morbidity. Death may result from complications related to extracutaneous involvement or adverse effects of therapy.

Clinical differential diagnoses include systemic sclerosis, scleredema, and nephrogenic systemic fibrosis. Other disorders characterized by sclerodermoid skin changes may also enter the differential diagnosis.

A localised form, known as papular mucinosis or lichen myxoedematosus, has a less severe course and lack systemic involvement. Patients with scleromyxedema in the absence of monoclonal gammopathy are considered to have a atypical form of the disease.

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Skin biopsy is essential for diagnosis. Scleromyxedema is characterized by a triad of microscopic features that includes deposition of mucin in the dermis, an increase in dermal collagen and proliferation of irregularly arranged fibroblasts. The epidermis may be normal or atrophic; the hair follicles may be atrophic, and a slight perivascular, superficial, lymphoplasmacytic infiltrate is often present. The elastic fibres are fragmented and decreased in number.

An interstitial, granuloma annulare-like pattern has been described in approximately 25 per cent of the cases. This histologic pattern is characterized by a diffuse, interstitial proliferation of histiocytes, giant cells, and lymphocytes within the papillary and mid-reticular dermis forming loose granulomas among collagen fibres and mucin deposits.

Although treatment of scleromyxedema is recommended to minimize risk for the development of complications, a paucity of high-quality studies on the efficacy of treatments for scleromyxedema and an incomplete understanding of the pathogenesis of the disorder have prevented the development of definitive guidelines on the best approach to treatment. No randomized trials have evaluated therapies for scleromyxedema. No specific treatment appears to be uniformly effective or curative, and the relative efficacies of the treatments that have been utilized remain unclear. As a consequence, opinions vary on the preferred approach to treatment. In all cases, consideration of the risk-benefit ratio of treatment is important for selecting an appropriate therapeutic regimen; both scleromyxedema and its therapies may induce life-threatening side effects.

Patients with scleromyxedema generally require systemic therapy. Intravenous immunoglobulin (IVIG) is recommended as initial treatment. Systemic glucocorticoids and immunomodulatory drugs (thalidomide or lenalidomide) are alternative treatment options that may also be used in conjunction with IVIG therapy. Patients who fail to respond to IVIG, systemic glucocorticoids, or immunomodulatory drugs may benefit from other therapies. Examples of treatment options for the severe and refractory diseases include bortezomib plus dexamethasone, autologous stem cell transplantation, and melphalan. Recurrence of scleromyxedema is common after withdrawal of effective therapy. Long-term maintenance treatment usually is required, and close clinical follow-up is necessary.

References

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After graduating from the University of Melbourne in 2006 with a MBBS and BMedSc, Dr Liu undertook her intern year at the Geelong Hospital. She completed her first year of training at the Peter MaCallum Cancer Centre in 2008, then continued her training in anatomical pathology at the Alfred Hospital until 2011. During this time, Dr Liu also participated in teaching duties at Monash.

In 2011, Dr Liu took up residency at Cabrini Hospital under the guidance of Dr William Downey, before spending her final year of training at the Western Hospital. After completing her training in late 2012, Dr Liu became a Fellow of the Royal College of Pathologists of Australasia and joined Melbourne Pathology in February 2013 as a Histopathologist. Dr Liu is a member of the American Society of Dermatopathology and the Australasian Dermatopathology Society. She is also involved in dermatology registrar teaching in Victoria.

Dr Liu is part of the Sonic SkinDx reporting team with a special interest in dermatopathology.