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Travis C. Sizemore, Gulzar Merchant, Katharine Whitfield

ABSTRACT

Introduction: Scleroderma is an autoimmune connective tissue disease characterized by pervasive systemic multiple organ fibrosis. Definitive diagnosis can be difficult as this disease has a highly variable disease spectrum and course. Further complicating matters, there exist several less commonly known imitators, termed pseudosclerodermas, which force a more open differential than might be presumed initially.

Case Report: We present the case of a 46-year-old female diagnosed with pseudoscleroderma.

Conclusion: This case emphasizes the importance of skin biopsy while not on steroids and also the need to maintain a broad differential even in the setting of biopsy results.
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Keywords: Pseudoscleroderma, Scleromyxedema, Scleroderma

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INTRODUCTION

Systemic sclerosis, known commonly as scleroderma, is an autoimmune connective tissue disease characterized by systemic multiple organ involvement with a highly variable disease spectrum and course. Exact etiology has yet to be elucidated, however, it is known that pathogenesis involves fibroblast dysfunction, autoimmune response with abnormal production of antibodies, and tissue hypoxia secondary to vascular abnormality [1]. Genetic involvement is also known to predispose patients to scleroderma, with genome-wide association studies illustrating the variable genetic components that contribute to the clinical sub-phenotypes of systemic sclerosis [2, 3]. The classification criteria for diagnosis was revised in 2013 by a collaborative initiative of the American College of Rheumatology/European League against Rheumatism (ACR-EULAR) and was shown to have improved sensitivity and specificity over the 1980 criteria set out by the ACR [4]. It includes a point system with weighted variables determined by multi-criteria decision analysis. There are two exclusionary criteria, one sufficient criterion, and seven criteria of varying weight in achieving a summative threshold score for classification of systemic sclerosis [4].

One of the exclusion criteria of the new initiative is that the scoring is not applicable to those with "a scleroderma-like disorder that better explains their manifestations." Narrowing the differential diagnosis is often difficult because of the existence of these less well known imitators of scleroderma. The term "pseudoscleroderma" is an umbrella term that has been used to describe skin lesions that imitate or resemble systemic sclerosis. We herein report a case of pseudoscleroderma. The patient, and a patient with diabetes with paraproteinemia initially presumed to be
scleroderma based on biopsy but not consistent with current diagnostic criteria of scleroderma.

**CASE REPORT**

A 46-year-old Caucasian female presented as a new patient at an Internal medicine resident rheumatology clinic with a nine-month history of swelling in her arms and legs. She stated that she had noticed a thickening/hardening of the affected skin and pain in her joints that had been progressively worsening over the last six months. She had recently been seen by an oncologist after a previous lab work revealed an elevated serum IgG level, and by their assessment, she had a very small elevation in a monoclonal protein which was not deemed to be clinically significant. However, this physician was concerned with the “plaque-like lesions” all over her body. She was then referred to dermatology for biopsy, which also occurred prior to being seen at the Rheumatology Clinic.

This patient had a past medical history of two DVT’s in 1997 and 2002 involving her left leg for which she is on Coumadin. She had recently been diagnosed with type 2 diabetes mellitus with a HgbA1c of 7.5%. She has hypertension, hyperlipidemia, and depression. She stated that throughout these months, she had not experienced any fever, dysphagia, or Raynaud’s-like symptoms. The patient was morbidly obese, but did report an involuntary weight loss of 50 lbs since her symptoms began.

On examination, she was afebrile with elevated blood pressure 197/113 mmHg, heart rate 83bpm, temperature 97.1°C, weight 163.48 kg, and BMI 56.44. Skin exam showed thick indurated skin across her thighs, calves, abdomen, upper arms, and lower arms that stopped proximal to the phalanges. All extremities were involved equally. There were also changes in pigmentation with both hypo- and hyperpigmentation scattered throughout affected areas. Scabbed-over ulcers were present mainly on bilateral thighs that were not erythematous or warm to palpation (Figures 1–6). Ophthalmic, cardiac, and pulmonary examinations were within normal limits.

Laboratory investigations reveal IgG was elevated at 1679 mg/dl, with normal IgE (<4 mg/dl), CRP 51.4 mg/dl, ANA negative, ASO<50 IU/ml, scleroderma and centromere antibodies negative, anti-smith and anti-RNP antibodies negative, kappa-lambda ratio normal at 0.52. Computed tomography (CT) scan of the thorax exhibited hepatomegaly and mediastinal, retroperitoneal, hepatic, and pelvic lipomatosis. PFTs were performed, showing mild airway obstruction with FEV1/FVC 68.

Two punch biopsies were obtained by the consulting dermatologist. Right proximal forearm biopsy findings were deemed insignificant, but histopathological examination of the sample from the right anterior proximal thigh (Figures 7 and 8) revealed extensive dermal fibroplasia with hyalinization and sparse perivascular lymphoplasmacytic inflammation suggestive of scleroderma. It did not show the degree of cellularity or mucin deposition typical of nephrogenic systemic fibrosis or scleromyxedema. An atypical lymphoid infiltrate was not seen. Basketweave orthokeratosis was observed. The vital epidermis was normal in thickness and architecture. Throughout the full thickness of the reticular dermis there was prominent fibrosis. There were sparse superficial perivascular inflammatory infiltrate of lymphocytes, mononuclear cells, and plasma cells.

These initial punch biopsies were taken while the patient was on prednisone. Upon visit at the clinic, the patient was set up for a deeper biopsy to the fascia of the thigh that was to be done with the patient off of all steroids. This biopsy revealed collagen thickening with decreased intra-collagenous clefts and a focal decrease in perieccrine fat. There were sparse patchy perivascular lymphoplasmacytic infiltrate present.

The limited fascial component is free of inflammatory elements and increased eosinophils are not seen. The overall features are morphologically often seen in scleroderma (Figures 9 and 10).

From the history, clinical examination, and histopathological findings, a diagnosis of nonspecific pseudoscleroderma was made and further evaluation and treatment of paraproteinemia was suggested.

**DISCUSSION**

Scleroderma was originally described by Neapolitan physician Carlo Curzi in a monograph dated 1752 [5]. The term is derived from the Greek words “sklerosis,” meaning hardness, and “derma,” meaning skin. Systemic sclerosis...
prevalence is estimated between 3 and 24 per 100,000 persons and appears to be higher in North America and Australia as compared to Europe and Japan [6].

Two distinct clinical subsets exist in scleroderma, determined by the degree of skin involvement: limited cutaneous systemic sclerosis with skin findings usually limited to the hands and forearm, and diffuse cutaneous systemic sclerosis that can involve abdomen, chest, upper arms, and shoulders.

Specific histological findings of scleroderma include an increased amount of new collagen synthesis in the reticular dermis as well as an increased number of myofibroblasts, activated fibroblasts that express the smooth muscle marker (smooth muscle actin), presence of myofibroblasts, with intima proliferation and...
parakeratosis [7, 8]. Serum antibodies, systemic sclerosis specific autoantibody-anticentromere antibodies, antitopoisozerase antibodies and anti-RNA polymerase III antibodies are found in over 50% of patients and can be useful predictors of disease prognosis and organ involvement [9].

Prognosis in systemic sclerosis is poor and often fatal, with 10 year survival ranging from 54–66% [10]. However, many of the causes of pseudoscleroderma syndromes have much favorable prognosis and can be reversed by treatment of the underlying etiology or removal of offending agent.

The term “pseudoscleroderma” is an umbrella term that has been used to describe skin lesions that imitate or resemble systemic sclerosis. These disorders typically occur as either distinct pathological entities or a complication of malignancy. A smaller number are induced by medication or environmental factors [11, 12]. To list a few: eosinophilic fasciitis, sclerodermitiform genodermatoses, scleredema adultorum of Buschke, acrodermatitis chronica atrophicans, porphyria cutanea
tarda, Graft-versus-host disease, nephrogenic fibrosing dermopathy (NFD), scleredema diabeticorum, and scleromyxedema. Pseudoscleroderma syndromes mimic scleroderma in general by causing thickening/hardening of the skin. Additional common factors of pseudoscleroderma include: Pathogenesis is thought to be secondary to activation of eosinophils and upregulation of fibroblast and collagen synthesis producing an overall increase in cytokines, specifically interleukin-4 and interleukin-13, as well as transforming growth factor beta [13].

It is often very difficult to differentiate from scleroderma and can result in delayed diagnosis and treatment. To be distinguished from scleroderma, the ACR/EULAR classification criteria have been adapted.

CONCLUSION

Herein, we report a case of nonspecific pseudoscleroderma, initially thought to be true scleroderma based on biopsy. However, patient did not meet diagnostic criteria for scleroderma. Although morphological features observed on patient’s histopathology can be seen in scleroderma, scleroderma is not a diagnosis based solely on pathology. In fact, ACR/EULAR updated classification criteria does not include pathology. The diagnosis of nonspecific pseudoscleroderma was made because clinically, patient did not meet criteria for scleroderma, having scored 0/34 points (Table 1). In addition, patient has concurrent paraproteinemia with elevated IgE that can be seen in different and distinct types of pseudoscleroderma. The patient’s clinical profile did not correspond completely with any one subset of pseudoscleroderma, thus, she was diagnosed with a nonspecific form pending further evaluation with bone marrow biopsy and flow cytometry and additional dermatologic evaluation. This case report is an important reminder that many rheumatological diseases cannot be made simply by pathology on biopsy but need to be taken within clinical context and case by case.

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Author Contributions
Travis C. Sizemore – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Gulzar Merchant – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Katharine Whitfield – Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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