An Unusual Case of Deep Localized Scleroderma in a Patient with Chronic Kidney Disease

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Localized scleroderma (LS) is a rare fibrosing disorder of skin and underlying tissues. Although it can affect all races, it has a higher prevalence in whites. Deep LS is the least common among seven LS variants, representing less than 5% of cases, and typically affects areas of pressure such as the hips and waist. We report a unique clinical case of bilateral lower extremity deep LS in a 51-year-old Puerto Rican woman with chronic kidney disease (CKD). In patients with CKD, it is important to distinguish LS from nephrogenic systemic fibrosis (NSF). Both can present with skin fibrosis and contractures over joints yet have significantly differing treatment approaches and prognosis. Our case report is unique due to the patient's Puerto Rican ethnicity, CKD history, and isolated anterior lower extremity involvement. In this report, we highlight key clinical and histopathological findings of LS, and how they differ from that of NSF.

Key words: Localized scleroderma, Morphea, Nephrogenic systemic fibrosis, Gadolinium, Kidney disease

Localized scleroderma (LS), or morphea, is a fibrosing connective tissue disease with worldwide prevalence of 0.4-2.7 per 100,000 and 3:1 female: male ratio (1, 2). Although the prevalence in the Hispanic/Latin American population is unknown, the largest cohort showed 10 (7.7%) of 123 adults with LS were Hispanic/Latin American (3). With seven different morphologies described, LS can affect the skin (superficial plaque and generalized morphea), deep structures including subcutaneous fat and muscle, (deep plaque and linear morphea), or both (mixed morphea). Similarly, the anatomical distribution may involve only trunk (plaque morphea), trunk, extremities, and face (linear morphea), or diffuse with sparing of hands and face (generalized morphea). Differential diagnoses of LS include systemic sclerosis (SSc), scleromyxedema, nephrogenic systemic fibrosis (NSF), and eosinophilic fasciitis (4). Unlike SSc, patients with LS do not have visceral organ involvement, Raynaud's phenomenon, or sclerodactyly (5, 6). In addition, anti-scleroderma-70 (anti-topoisomerase-I) and anti-centromere-B antibodies are usually positive in patients with SSc, but not LS (3, 7). Anti-nuclear antibodies (ANA) are less specific and positive in 23-68% of LS cases (7). In patients with CKD, it is important to distinguish LS from NSF given their differing treatments and prognosis. While there is no single gold-standard test for diagnosing LS, the clinical presentation, medical history, risk factors, autoantibodies, and histopathology encompass the diagnosis (2, 8). We report the first case, to our knowledge, of deep LS with isolated bilateral lower extremity involvement in a middle-aged Puerto Rican woman with CKD.

Case Report

A 51-year-old woman presented to our private dermatology clinic with painful bilateral lower leg plaques of two months duration. On examination, severely indurated, tender plaques were localized mid-thigh downwards with peau d'orange edema and leukoderma discoloration (Figure 1). Past medical history included stage 5 CKD (GFR<15mL/min) on peritoneal dialysis, hypertension, type 2 diabetes mellitus, and psoriasis. No Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, or nailfold capillary changes were present. She reported treatment with erythropoietin (EPO) years ago but denied gadolinium (Gd) exposure. Punch biopsy of left lower extremity lesion and laboratory workup for SSc were performed (Table 1). Laboratory analysis revealed positive Speckled Antinuclear Antibody, elevated Erythrocyte Sedimentation Rate (ESR) (52mm/hr [reference: 0-29mm/hr]), and negative Antiscleroderma-70 (anti-topoisomerase-1) and anti-centromere-B antibodies. Biopsy revealed thickened dermis with collagen bundles, sparse perivascular lymphocytic

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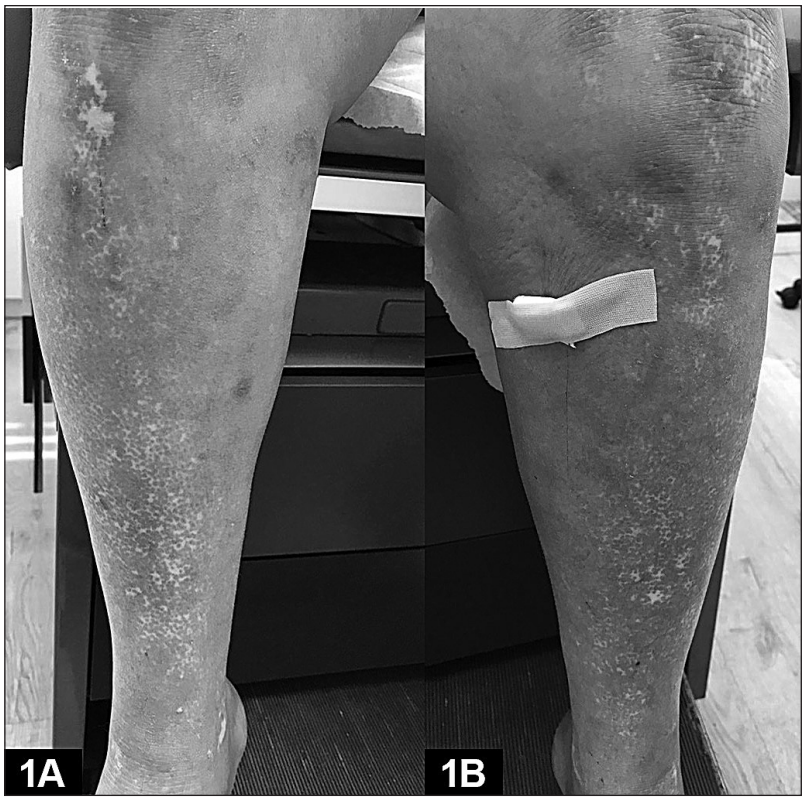

Figure 1A-B. Deep Localized Scleroderma. Severely indurated, tender, with leukoderma discoloration and peau d'orange edema areas on bilateral legs.

infiltrates, plasma cells, straight lateral edges ("square biopsy" sign characteristic of scleroderma), and absence of adnexal structures (Figure 2). Mucin stain was negative and CD34 immunohistochemistry was normal. Since NSF would show CD34+ cells and dermal mucin deposition, the diagnosis of LS was favored (Table 1) (8). In addition, the biopsy revealed sparse perivascular lymphocytic infiltrate with plasma cells, most consistent with scleroderma (9, 10). The patient had received Ultraviolet-A (UVA) phototherapy at another clinic for two months without improvement. On follow-up six months later, the lesions had progressed proximally up the patient's thighs, further limiting mobility (Figure 3). After a careful literature review, we determined that the best treatment plan was methotrexate 7.5mg once a week and prednisone 20mg once daily (9). Two days after taking her first dose, the methotrexate was discontinued due to adverse events. The patient was subsequently hospitalized due to CKD progression and further dialysis requirements and received no further follow-up at our clinic.

Table 1. Clinical and histopathological criteria for our case's differential diagnosis of LS, SSc, and NSF (1-3, 5-8).

Criteria	LS	Our Case	SSc
Anatomical regions	Trunk, lower extremities, or diffuse	Lower extremities	Lungs, esophagus, fingertips, and face
History of Psoriasis	12% positive	Positive	<2% positive
Anti-nuclear antibodies	23–68% positive	Positive	90% positive
Anti-scleroderma-70	<3% positive	Negative	60% positive
Anti-centromere B	<1% positive	Negative	95% positive
Criteria	**LS**	**Our Case**	**NSF**
Visceral organs involved	Negative	Negative	Positive
History of Gd exposure	Negative	Negative	Positive
History of EPO exposure	Negative	Positive	Positive
CD34+ spindle cells	Negative	Negative	Positive
Dermal mucin deposition	Negative	Negative	Positive

EPO = Erythropoietin; Gd = Gadolinium; LS = Localized scleroderma; SSc = Systemic scleroderma; NSF = Nephrogenic systemic fibrosis

Discussion

LS has multifactorial etiology and risk factors include trauma, radiation, drugs, infection, and autoimmunity (1). Our patient suffered from a rare LS presentation with deep tissue involvement extending to the lower extremities bilaterally. The deep form of LS represents less than 5% of cases (9). NSF has been associated with prior EPO and Gd-containing contrast in patients with renal failure (11, 12). Since our patient had history of CKD and EPO, but not Gd, exposure, NSF was suspected (Table 1). NSF lesions most frequently affect lower extremities symmetrically and may involve the trunk (11, 13). As in deep LS, NSF may present with peau d'orange edema, wood-like indurated areas, and joint contractures (11). However, the most significant finding when suspecting NSF is impaired renal function (11, 13). Laboratory tests are not specific for NSF and are primarily used to rule out other conditions, such as SSc (11).

Histopathologic examination of NSF frequently includes thickened collagen bundles separated by clefts, mucin deposition, and fibroblast and elastic fiber proliferation (12). The cellular infiltrate is composed of CD34+ spindle cells and procollagen-I-producing cells with stellate or epithelioid appearance (11). In our patient, mucin test was negative and CD34 staining in blood vessels was consistent with normal findings, supporting the LS diagnosis over NSF. Although SSc and LS cannot be distinguished by histopathology, SSc was ruled out due to absence of systemic symptoms and negative Antiscleroderma-70 and Anti-Centromere-B antibodies (14, 15). Nonetheless, the

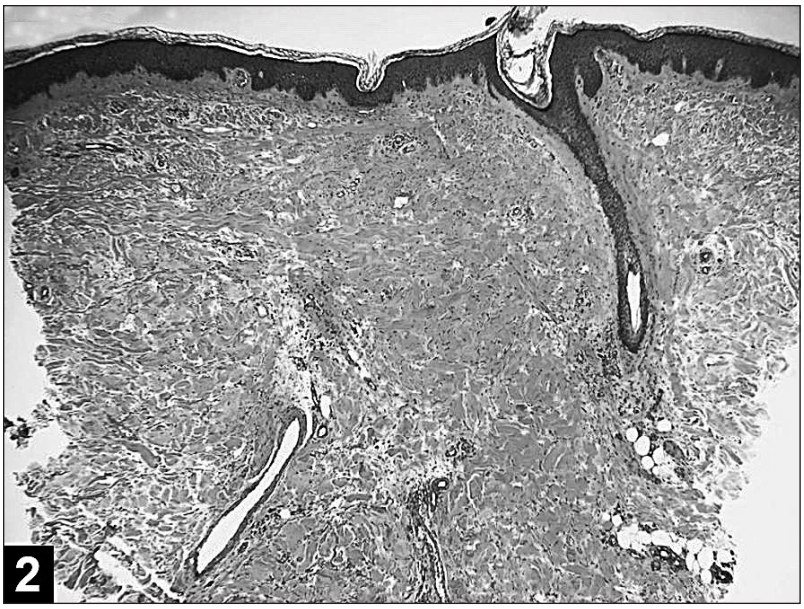

Figure 2. Deep Localized Scleroderma. "Square biopsy" showing dermal sclerosis and absence of most adnexal structures (H&E, 10x magnification) Plasma cells can be identified within the inflammatory cell infiltrate.

speckled antinuclear antibody test was positive and ESR was elevated. These laboratory findings and histopathology results supported the deep LS diagnosis (10). Deep LS occurs most commonly in pressure-bearing joints of the trunk such as hips and waist (1, 9). Our patient's clinical presentation of Deep LS is unique due to Puerto Rican ethnicity, CKD history, and isolated lower extremity involvement.

Mild LS may be managed with topical and/or UVA therapy, while severe disease may require methotrexate and systemic corticosteroids (9). A recent study showed 81% of hydroxychloroquine-treated patients experienced improvement, proposing a potential treatment when immunosuppressants are contraindicated (14). In contrast to LS, NSF does not improve with corticosteroids or other immunosuppressive drugs, and treatment is focused on kidney function optimization (9, 15).

Conclusion

In patients with CKD and suspected NSF, it is vital to maintain a high suspicion index for deep LS and repeat testing, especially in patients with indurated plaque progression, resulting in poor quality of life and impaired mobility. We present a case of a Puerto Rican woman with a history of CKD and isolated lower extremity lesion distribution initially suspected to be NSF but later diagnosed with LS. Thorough laboratory workup and biopsy were necessary to detect histopathologic findings supporting our patient's ultimate diagnosis. This case describes challenges of diagnosing and treating a patient with CKD and LS, including the importance of repeat evaluations, potential for poor response to UVA therapy, and need to consider timely treatment progression to systemic treatment with methotrexate and prednisone if indicated (9, 15).

Resumen

La esclerodermia localizada (EL) es una condición rara que provoca fibrosis de la piel y tejidos subyacentes. Aunque puede afectar a todas las razas, la EL tiene mayor prevalencia en los blancos. La EL profunda es la menos común entre siete variantes, representando menos del 5% de los casos. La misma, normalmente afecta áreas del cuerpo que sostienen peso como las caderas y cintura. Reportamos un caso de EL profunda bilateral en las extremidades inferiores de una mujer puertorriqueña de 51 años con enfermedad renal crónica (ERC). En pacientes con ERC, es importante distinguir la EL de la fibrosis sistémica nefrogénica (FSN). Ambas condiciones pueden presentar fibrosis en piel y articulaciones subyacentes, pero poseen tratamientos y pronósticos distintos. Nuestro caso es único debido a la etnicidad puertorriqueña, historial de ERC, y lesiones exclusivamente en extremidades inferiores de la paciente. Además, presentamos diferencias clínicas e histopatológicas entre la EL y la FSN.

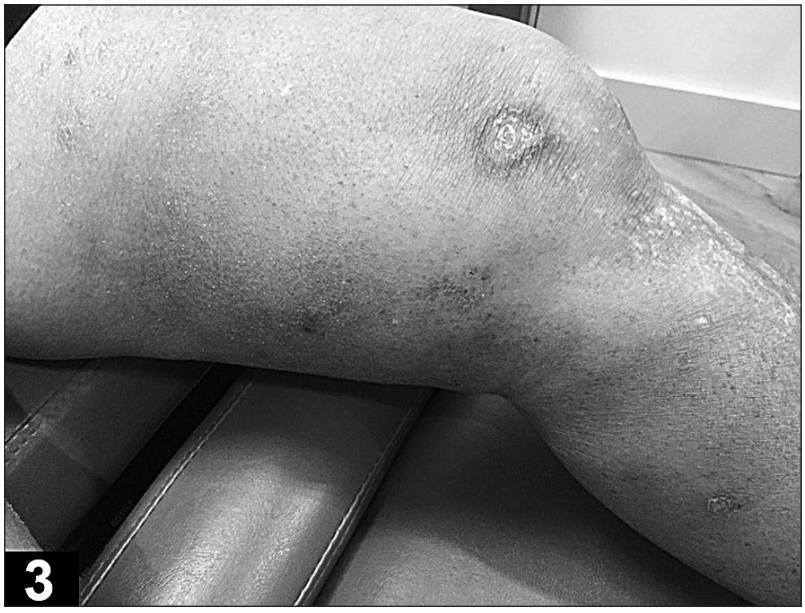

Figure 3. Deep Localized Scleroderma. Lesions had spread proximally up the patients' thighs, further limiting mobility, during follow up evaluation 6 months later.

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