International Journal of Research in Dermatology
Colando S et al. Int J Res Dermatol. 2022 Jan;8(1):116-119
http://www.ijord.com

DOI: https://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20214921

Case Report

Granulomatous slack skin with hypercalcemia indolently mimicking sarcoidosis

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Received: 25 October 2021
Revised: xx March 2021
Accepted: 07 December 2021

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ABSTRACT

Granulomatous slack skin is a rare variant of cutaneous T-cell lymphoma characterized by lax skin and granulomatous infiltrate with loss of elastic fibers on histology. We report a unique case of a female presenting with CD30- granulomatous slack skin complicated by hypercalcemia, initially diagnosed, and managed as sarcoidosis. Interestingly, she had a history of previously treated CD30+ cutaneous T-cell lymphoma. Granulomatous slack skin can frequently mimic other benign and malignant cutaneous diseases, prompting the need for clinical vigilance from dermatologists.

Keywords: Granulomatous slack skin, Cutaneous T-cell lymphoma, Mycosis fungoides, Hypercalcemia

INTRODUCTION

Granulomatous slack skin (GSS) is a rare variant of cutaneous T-cell lymphoma (CTCL) characterized by lax skin and granulomatous infiltrate with loss of elastic fibers on histology. As GSS is a rare and slowly progressing condition which can mimic other benign and malignant cutaneous diseases, misdiagnosis and delays in treatment can occur. GSS typically follows an indolent clinical course, but in some cases can progress into secondary lymphomas prompting the need for accurate diagnosis and close monitoring by dermatologists and a multidisciplinary team. We present a clinical report of a unique case of a 65-year-old female diagnosed with GSS complicated by hypercalcemia, initially diagnosed, and managed as sarcoidosis.

CASE REPORT

Five years ago, a 65-year-old Haitian American female presented with pruritic, painful cutaneous lesions appearing on the proximal pretibial areas. She had a prior history of rheumatoid arthritis and cutaneous sarcoidosis with hypercalcemia that had been managed with prednisone, methotrexate, and hydroxychloroquine by rheumatology for several years. Physical examination at the time revealed tender, erythematous, and violaceous nodules distributed on the pretibial region and upper posterior arms. Punch biopsy results from the pretibial lesions revealed infiltration of plump amphophilic cells with abundant cytoplasm and irregular vesicular nuclei. Immunohistochemistry analysis was positive for CD30, resulting in a diagnosis of primary cutaneous CD30+ T cell lymphoma. Human T lymphotropic virus type-1 (HTLV-1) and human-immunodeficiency virus (HIV) were ruled out by serology testing. Analysis of clonality detected monoclonal T-cell receptor gamma (TCR) gamma gene rearrangements. Peripheral blood flow cytometry analysis revealed a mixed population of maturing myeloid cells with no abnormal maturation. Positron emission tomography (PET) scan demonstrated multiple subcutaneous and cutaneous nodules in the extremities

representing the known primary cutaneous T cell lymphoma. Over a course of two years, she was managed by a team of dermatologists, rheumatologists, and hematology-oncologists and was treated with topical steroids, rituximab, chlormethine, paclitaxel, and brentuximab. Of note, she also had subsequent breast cancer treated with chemotherapy and radiation during her rituximab therapy, and currently remains in remission. Her cutaneous symptoms were completely resolved after treatment.

Two years later, at the time of this consultation, the patient presented with new worsening cutaneous patches and plaques, as well as hypercalcemia. Lesions were located on the dorsal hands, buttocks, thighs, upper back, and the chest. She was applying triamcinolone 0.1% cream twice daily as advised from rheumatology until her dermatology consultation. Physical exam findings included erythematous, violaceous, and flesh-colored atrophic patches and plaques with peripheral scale and a sagging appearance of the skin (Figures 1 and 2). The clinical differential diagnosis included cutaneous T cell lymphoma, cutaneous sarcoidosis, and lupus erythematosus, amongst other conditions. Three 4mm punch biopsies were obtained. All three punch biopsy specimens revealed patchy lichenoid infiltrates within upper dermis, slight psoriasiform hyperplasia of the epidermis, wiry bundles of collagen and epidermotropism (Figure 3).

Figure 1: Erythematous, violaceous, and atrophic patches and plaques with sagging lax skin.

Within the deeper dermis there was a nodular and interstitial granulomatous infiltrate of histiocytes with numerous multinucleated giant cells and loss of elastic fibers (Figure 4). Immunohistochemistry analysis was positive for CD3 and negative for CD30. These histopathological findings are consistent with the diagnosis of the granulomatous slack skin variant of cutaneous T cell lymphoma. Angiotensin converting enzyme (ACE), rheumatoid factor (RF), and antinuclear antibodies (ANA) were within normal limits. PET scan again revealed only cutaneous and subcutaneous nodules with no evidence of further systemic involvement.

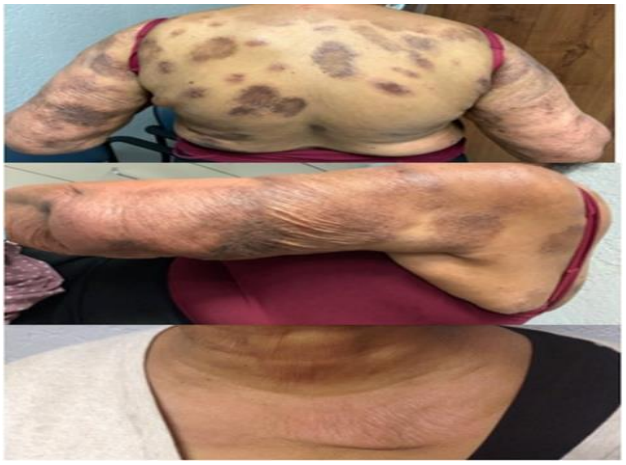

Figure 2: Erythematous, violaceous, and atrophic patches and plaques with sagging lax skin.

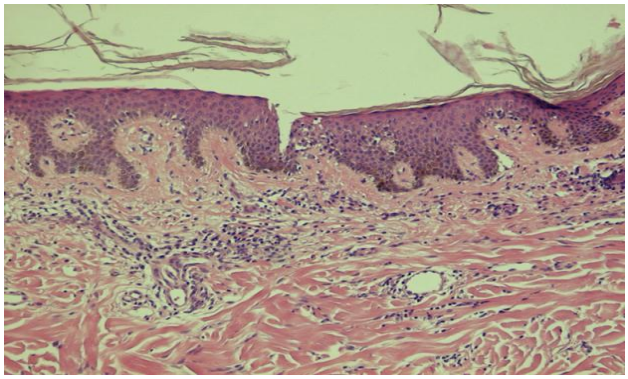

Figure 3: H&E 4x demonstrating patchy lichenoid infiltrates, wiry bundles of collagen, and exocytosis consistent with mycosis fungoides.

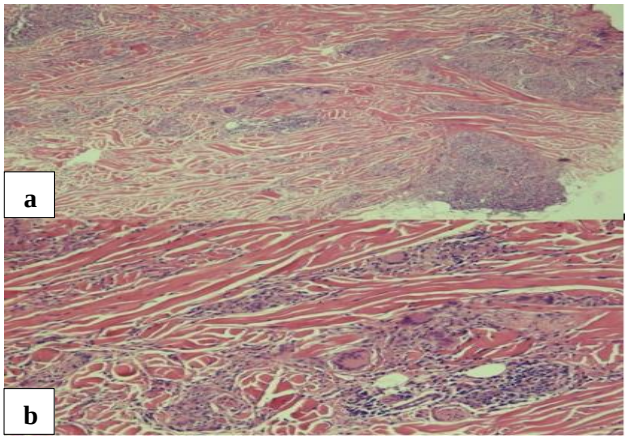

Figure 4: H&E, (a)-4x and (b)-10x, demonstrating deep dermal nodular and interstitial granulomatous infiltrate of histiocytes with numerous multinucleated giant cells and loss of elastic fibers.

DISCUSSION

GSS is a rare variant of CTCL which according to the World Health Organization-European Organization for

Research and Treatment of Cancer (WHO–EORTC) classification update of 2018, accounts for less than 1% of primary cutaneous lymphomas.[1] GSS is predominantly found in males age 30-40.[2] Physical exam findings reveal hardened erythematous plaques predominantly localized in the flexural areas which progress overtime to become pedunculated.

In the early stages of disease progression, the GSS closely resembles granulomatous mycosis fungoides (GMF) and must be differentiated clinically, as these two conditions cannot be differentiated solely on histopathology.[3] The hallmark of pedunculated lax skin and diffuse elastophagocytosis is a key clinical differentiating factor predominantly seen in GSS.[4] Clinical differential diagnoses include anetoderma and cutis laxa which are also characterized by loose skin, however unlike these diseases, GSS demonstrates a granulomatous infiltrate.

On histology, GSS is characterized by a bandlike infiltrate of lymphocytes, granulomatous infiltrate with multinucleated histiocytic giant cells in the deeper dermis with elastophagocytosis. In chronic lesions, there is a diffuse loss of elastic fibers, which can be illustrated using elastin stains.[5] Similar to mycosis fungoides, the immunohistochemical profile is characteristically CD3+, CD4+, CD8-, CD30-, and CD20-.[5] In rare cases, immunoreactivity has been reported positive for CD30.[2,6,7] Interestingly, our patient had a history of previously treated CD30+ CTCL, however currently presented with CD30- disease. Most cases demonstrate clonal rearrangement of TCR genes, which can be helpful for diagnosis in early stages of the disease.[8]

Although commonly detected in granulomatous diseases such as sarcoidosis, hypercalcemia is a rare finding in GSS.[9] Extrarenal production of α_1 hydroxylase enzyme to increase vitamin D production has been projected as the pathogenesis behind hypercalcemia in GSS.[10] In the four reported cases in literature reviews, all of the patients with hypercalcemia secondary to GSS were males.[9-12] To our knowledge, our case report is the first female with GSS complicated by hypercalcemia. It is reasonable to believe our patient's previously diagnosed sarcoidosis was GSS as both are granulomatous conditions which can present with hypercalcemia.

Several therapy options are available to GSS patients depending on the severity of disease, but their efficacy remains limited, and a definitive treatment remains unknown. Therapy options include surgical excision, chemotherapy, topical or systemic steroids, psoralen and ultraviolet A radiation (PUVA) therapy and nitrogen mustard. Despite GSS not having a therapeutic cure, the disease has a very slow, indolent course. WHO-EORTC indicates GSS has a 100% frequency of a 5 year survival.[1] Due to the high occurrence of secondary lymphoproliferative diseases with GSS, patients should be closely monitored long term for Hodgkin and non-Hodgkin lymphomas.[2]

CONCLUSION

In conclusion, we report a unique case of a female presenting with CD30- GSS complicated by hypercalcemia, initially diagnosed, and managed as sarcoidosis. Interestingly, she had a history of previously treated CD30+ CTCL. Although hypercalcemia has been reported in GSS in males, this is the first report to our knowledge of this finding in a female. Consistent with the cases reported in the literature, the pathognomonic finding of pendulous skin and diffuse loss of elastic fibers supports our diagnosis of GSS in this patient. GSS can frequently mimic other benign and malignant cutaneous diseases, prompting the need for clinical vigilance from dermatologists to avoid misdiagnosis and delays in treatment.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Colando S, Seyffert J, Rivlin D. Granulomatous slack skin with hypercalcemia indolently mimicking sarcoidosis. Int J Res Dermatol 2022;8:116-9.