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Granulomatous slack skin. Histopathology diagnosis preceding clinical manifestations by 12 years.

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Abstract

Background: Granulomatous slack skin is a very rare subtype of T-cell cutaneous lymphoma, characterized by the slow development of cutaneous sagging, especially on flexural areas. Its behavior is indolent and the treatment, in the majority of cases, disappointing.

Main observations: We report a 54-year-old black patient with granulomatous slack skin, who at the beginning of the investigation showed intense xeroderma and generalized lymph node enlargement. The diagnosis was established based on histopathologic findings long before the disease's characteristic clinical presentation appeared.

Conclusion: During the twelve years of follow-up, the clinical manifestation evolved to marked skin looseness, most predominant in flexural regions, illustrating the clinical hallmark of granulomatous slack skin, long after first histological abnormalities were observed. (*J Dermatol Case Rep*. 2012; 6(4): 108-112)

Introduction

Granulomatous slack skin (GSS) is an extremely rare subtype of T-cell cutaneous lymphoma, characterized by the slow and progressive development of sagging skin of redundant aspect, especially in the flexural areas, such as the axillary and inguinal region.[1,2] Histology reveals monoclonal T-cell infiltrate of varying intensity, generally seen around deep and superficial vessels, sometimes occupying the upper dermis diffusely, associated with the presence of macrophages and multinucleated giant cells. These giant cells contain multiple nuclei and host lymphocytes or elastic fibers in their cytoplasm. Epidermothropism may be present or not and the reduction or absence of elastic fibers can be demonstrated by orcein stain.[3-5] Its clinical course is indolent and treatment is most often disappointing. In over 50% of cases, there is association with Hodgkin's disease.[6]

We describe a case of this rare entity whose diagnosis, based on its histopathology, was already considered years before the appearance of characteristic clinical manifestations.

Case Report

A 54-year-old black male patient, was sent to the Dermatology Out-Patient Clinic of the Clementino Fraga Filho University Hospital (HUCFF/UFRJ) 12 years ago, with intense ichthyosiform xeroderma, edema of the lower limbs associated with large mobile and painless adenomegaly in the cervical, axillary and inguinal chains. He was skinny and complained of fatigue, abdominal pain and vomiting. Endoscopy of the upper digestive tract was positive for *H. pylori* pangastritis. The digestive symptoms improved with ranitidine, 300 mg/day. All additional examinations carried out as complete blood cell count, biochemistry and chest X-ray, resulted within normality. The HIV and HTLV-I and II serology tests were negative. The abdominal and pelvic computerized tomography showed retroperitoneal adenomegaly and the hemosedimentation rate was very high (150 mm). The skin biopsy of the abdominal region demonstrated dense confluent lymphocytic infiltrate, occupying the dermis upper portions, focal epidermothropism, in addition to

multinucleated giant cells, some containing lymphocytes or elastic fibers. (Fig. 1, 2 and 3) The orcein stain showed marked decrease of elastic fibers in the dermis, which led to the histopathologic diagnosis of granulomatous cutis laxa, with differential diagnosis of granulomatous mycosis fungoides (GMF).

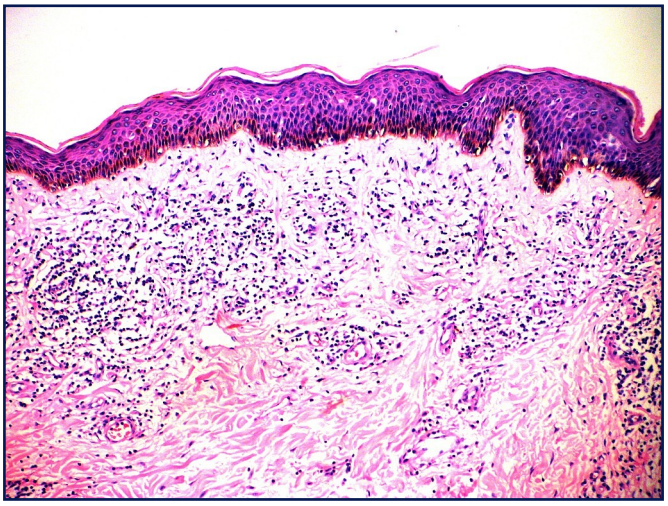

Figure 1
Confluent lymphocytic infiltrate, occupying the upper dermis portions (H & E, 40 x).

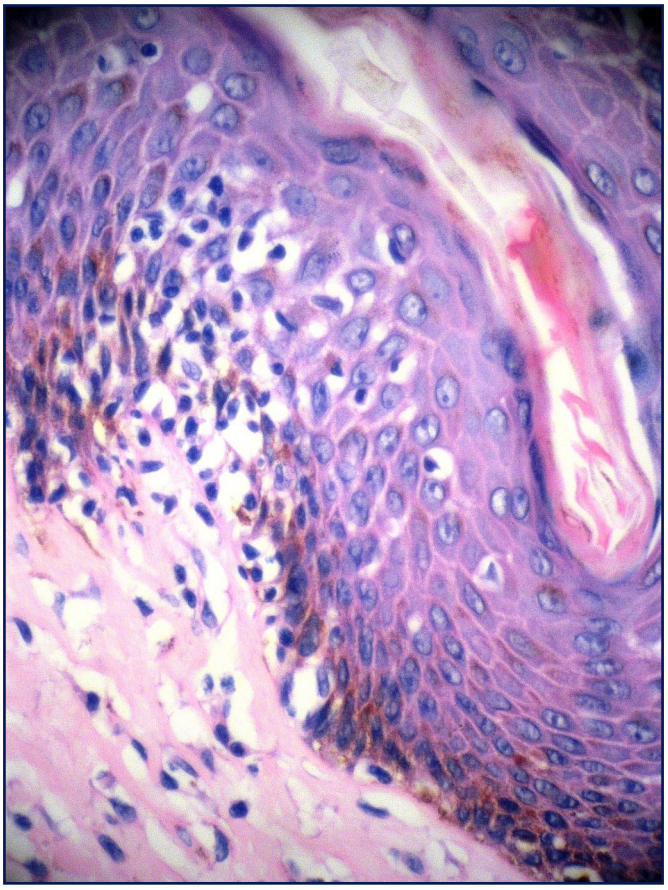

Figure 2
Focal epidermothropism (H & E, 100 x).

Histopathologic examination of the cervical lymph node demonstrated numerous sarcoid granulomas, comprising multinucleated giant cells with refringent phagocytosed material and epithelioid histiocytes. The lymphnode parenchyma was basically composed by small lymphocytes (CD3+), among which CD8+. Small B-lymphocytes (CD20+) and rare large lymphocytes (CD30+) were also observed. Numerous granulomas were present in the perilymphnode connective tissue, distinguishing the diagnosis from sarcoidosis.

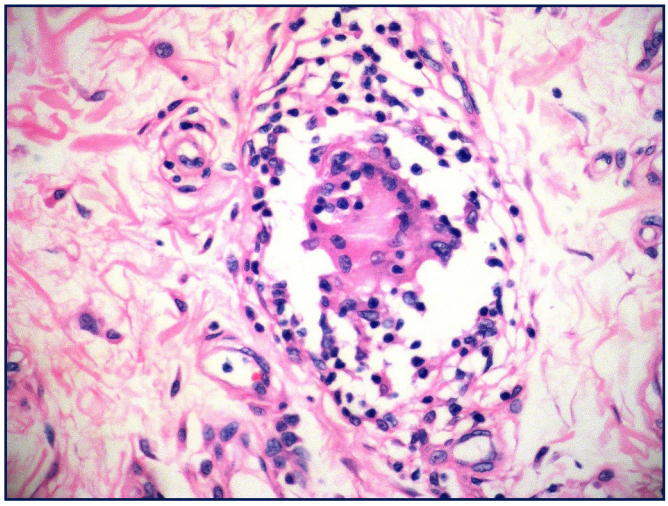

Figure 3
Multinucleated giant cells (H & E, 100 x).

Over twelve years of ambulatory follow up, it was possible to observe the clinical evolution to a pronounced skin laxity, predominantly in the axillary folds and occipital region (Fig. 4, 5), maintaining a xeroderma picture, confirming the clinical diagnosis and histopathologic granulomatous cutis laxa. The patient has been consulting the Dermatology and the Hematology Sectors, having already been submitted to several therapeutic attempts, as PUVA alone and associated with interferon alpha, localized radiotherapy and chemotherapy with gemcitabine, all of them without satisfactory improvement. After seven years from the beginning of the first symptoms, we noticed the development of tumor mass with multiple fistulous orifices in the medial side of the right inner thigh (Fig. 6), which, at histopathology, showed a high level progression to non-Hodgkin large T-cells lymphoma, revealing positivity for CD30 of the neoplastic cells and high index of cellular proliferation in immunohistochemical study. Then, a new chemotherapy scheme with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) was used leading to tumor involution, but without changes to the granulomatous cutis laxa. Currently, the patient is only kept under regular clinical monitoring with topical corticosteroids and emollients and eventual surgical removal of large subcutaneous lymphomatous masses that impacted on his quality of life.

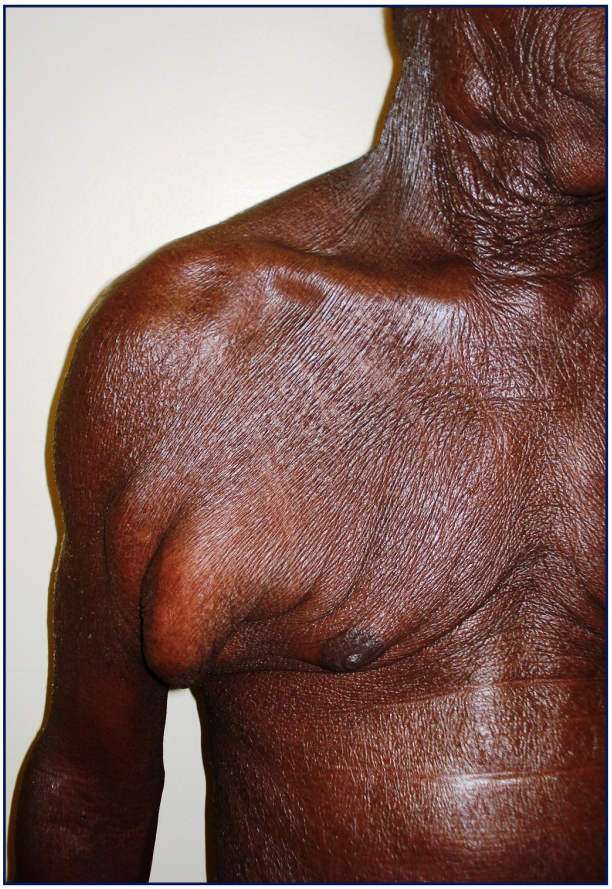

Figure 4
Marked cutis laxa skin laxity in the axillary region and cervical adenopathy.

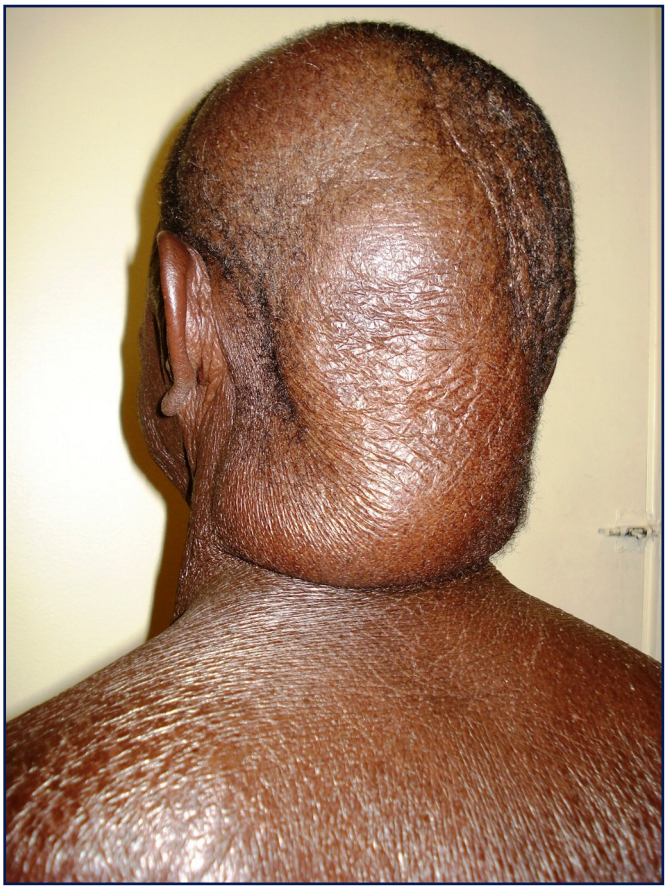

Figure 5
Cutis laxa skin laxity in the occipital region.

Discussion

In 1973, Convit *et al*. described for the first time a dermatosis that presented hardened plaques with features of cutis laxa in a 15-year-old boy. Histopathologically, these lesions presented granulomatous infiltrate throughout the dermis. The condition was named as chronic progressive atrophying granulomatous dermo-hypodermitis. This patient died of Hodgkin's disease after 20 years.[7] The granulomatous cutis laxa term was suggested by Ackerman, after reviewing the case in 1978.[5] Nine years later, Le Boit *et al*. demonstrated the nature of the lympho-proliferative disease and suggested that this would be a peculiar form of cutaneous T-cell lymphoma closely related to mycosis fungoides.[4] According to recent consensus at WHO-EORTC, GSS is classified as a rare subtype of mycosis fungoides with indolent clinical behavior.[8,9]

GSS is characterized by the appearance of erythematous or violaceous painless plaques, with atrophic surface, sometimes with mild desquamation. It generally affects the axillary and inguinal regions. The extracutaneous disease, especially in the spleen and lymph nodes, occurs less frequently. Bronchial mucosal infiltration may occur.[10] The size of the plaques increases slowly and progressively within a few years, leading to

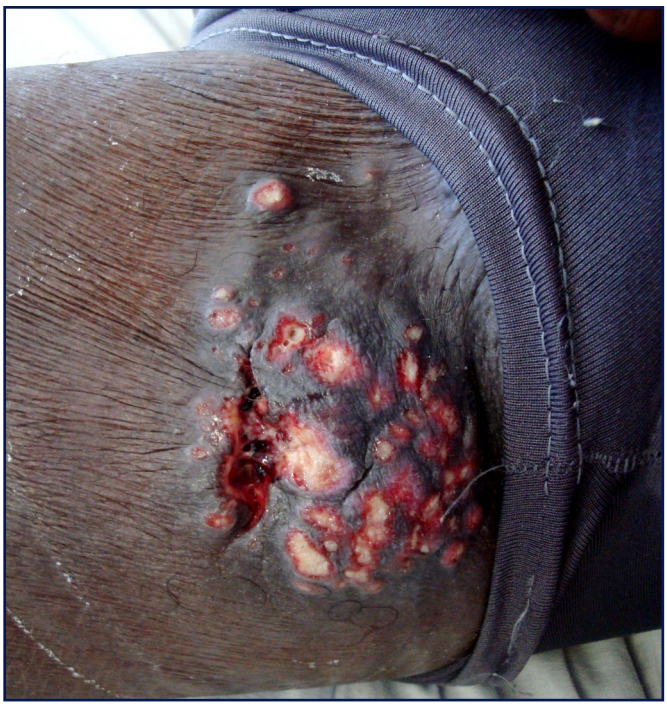

Figure 6
Tumor with multiple fistulous orifices in the right internal thigh.

redundant folds of loose skin. Ulceration may sometimes occur. GSS may affect all ages and sexes though predominant in males.[1,6,11] The average period for appearance of the disease is variable. Although GSS description in Caucasians predominates, there are reports in patients from Asia and India.[12] The black skin of our patient may have masked the flexural erythematous plaques described in the literature as preceding the subsequent skin laxity.

In histopathology, GSS presents lymphocytic infiltrate located predominantly in the papillary dermis, besides the presence of multinucleated giant cells and/or non-caseating granulomas. A characteristic finding of this entity is the presence of giant cell phagocyting elastic fibers (elastophagocytosis). The reduction or absence of elastic fibers can be demonstrated by orcein stain. The histological findings sometimes reach the whole extension of the dermis, even extending to the subcutaneous cellular tissue. Immunohistochemical studies demonstrate that the lymphocytic infiltrate has a predominance of CD4+, CD45RO+ and CD30+ cells and that there is a loss of T-cell markers such as CD3, CD5 and CD7.[1,5,8,13]

GMF has been described as the differential diagnosis for GSS. A multicentric recent study conducted by WHO/EORTC concluded that striking clinical differences exist between these two entities, but their histological findings overlap. It is therefore not possible to distinguish them only on histopathological basis. The looseness of the skin in flexural areas is found only in GSS. The presence of elastophagocytosis is more characteristic of GSS, however, it can also be observed in GMF.[8] In our case, histopathology revealed multinucleated giant cells phagocyting elastic fibers, and the possibility to follow up the same patient for years allowed us to check the development of skin laxity in fold areas and conclude the histological and clinical diagnosis of GSS.

GSS does not entail life-threatening risks, but its prognosis is defined by the development of lympho-proliferative concomitant diseases, such as Hodgkin disease, non-Hodgkin lymphoma, fungoides mycosis, acute myelogenous leukemia and Langerhans cell histiocytosis, in this order of frequency. This concomitance is very frequent, reaching 50%, according to some authors. The transformation into large cells lymphoma is also described in these patients, which is often mistakenly interpreted as the emergence of another concomitant lympho-proliferative neoplasia.[6,8-10,14] We believe that such transformation occurred in our patient.

Multiple therapeutic alternatives for GSS have been described, such as topical and systemic corticosteroids, PUVA, radiotherapy, multidrug therapy, immunosuppressive agents such as azathioprine, immunomodulators such as interferon alpha, as well as combined therapies. None of these therapies, however, present sustained satisfactory results. The surgical removal of redundant skin with aesthetic and functional purposes tends to relapse.[1,2,6,8,11] In our case, the response to isolated PUVA and associated with interferon alpha, chemotherapy with gemcitabine and localized radiotherapy at different times had partial and temporary result. The development into high level large T-cells non-Hodgkin lymphoma found in our patient's inner right thigh tumor has shown a good response to the CHOP scheme.

Conclusion

GSS is a rare disease. According to our experience, this is the third case diagnosed in 33 years at the HUCFF/UFRJ. It is important to emphasize that the opportunity of following up the patient over twelve years allowed us to observe the installation and a better characterization of this entity, which initially showed to be incipient. Only after many years it was possible to accompany the emergence of cutaneous folds redundancy, which is so typical of this entity, given that, at the beginning, the patient only presented intense xeroderma and generalized lymphadenopathy. The initial lymph node biopsy suggested sarcoidosis due to the presence of granulomas. Only the correlation of the clinical and the histological cutaneous findings allowed the redirection of the diagnosis towards T-cell cutaneous lymphoma. Clinical follow-up for a long period of time was also necessary for the final characterization of GSS and its development into high level T-cell cutaneous lymphoma.

Likewise as described in the consulted literature, our experience with the various therapeutic attempts was very frustrating.

References

1. Balus L, Bassetti F, Gentili G. Granulomatous slack skin. *Arch Dermatol*. 1985; 121: 250-252. PMID: 3977343.
2. Teixeira M, Alves R, Lima M, Canelhas A, Rosario C, Selores M. Granulomatous slack skin. *Eur J Dermatol*. 2007; 17: 435-438. PMID: 17673389.
3. Tsang WY, Chan JK, Loo KT, Wong KF, Lee AW. Granulomatous slack skin. *Histopathology*. 1994; 25: 49-55. PMID: 7959645.
4. LeBoit PE, Zackheim HS, White CR Jr. Granulomatous variants of cutaneous T-cell lymphoma. The histopathology of granulomatous mycosis fungoides and granulomatous slack skin. *Am J Surg Pathol*. 1988; 12: 83-95. PMID: 3257655.
5. Ackerman A. Granulomatous slack skin. In: Ackerman A. ed. Histologic diagnosis of inflammatory skin diseases. Philadelphia: Thomas Jefferson University 1978: 483-485.
6. Noto G, Pravatà G, Miceli S, Aricò M. Granulomatous slack skin: report of a case associated with Hodgkin's disease and a review of the literature. *Br J Dermatol*. 1994; 131: 275-279. PMID: 7917995.
7. Convit J, Kerdel F, Goihman M, Rondon AJ, Soto JM. Progressive, atrophying, chronic granulomatous dermohypodermitis. Autoimmune disease? *Arch Dermatol*. 1973; 107: 271-274. PMID: 4685583.
8. Kempf W, Ostheeren-Michaelis S, Paulli M, et al. Granulomatous mycosis fungoides and granulomatous slack skin: a multicenter study of the Cutaneous Lymphoma Histopathology Task Force Group of the European Organization for Research and Treatment of Cancer (EORTC). *Arch Dermatol*. 2008; 144: 1609-1617. PMID: 19075143.
9. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. 2005; 105: 3768-3785. PMID: 15692063.
10. Le T, Pierard G. Granulomatous slack skin syndrome and Hodgkin's disease. *Ital Gen Rev Dermatol*. 1986; 23: 48-49.

11. van Haselen CW, Toonstra J, van der Putte SJ, van Dongen JJ, van Hees CL, van Vloten WA. Granulomatous slack skin. Report of three patients with an updated review of the literature. *Dermatology*. 1998; 196: 382-391. PMID: 9669112.

12. Pai K, Rao R, Devadiga R, Shenoi S, Pai S. Granulomatous slack skin. *Int J Dermatol*. 2000; 39: 374-376. PMID: 10849132.

13. Burg G, Kempf W, Cozzio A, et al. WHO/EORTC classification of cutaneous lymphomas 2005: histological and molecular aspects. *J Cutan Pathol*. 2005; 32: 647-674. PMID: 16293178.

14. Miyagaki T, Sugaya M, Minatani Y, Fujita H, Hangaishi A, Kurokawa M, Takazawa Y, Tamaki K. Mycosis fungoides with recurrent Hodgkin's lymphoma and diffuse large B-cell lymphoma. *Acta Derm Venereol*. 2009; 89: 421-422. PMID: 19688163.