

Granulomatous slack skin: a case report demonstrating the evolution of the 16-year clinicopathological features that confuses with leprosy at its early stage.

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ABSTRACT :

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A middle-aged Thai male suffered from granulomatous slack skin (GSS), a rare subtype of mycosis fungoides (MF), whose benign clinical course was exemplified by an exceedingly long evolution of skin lesions taking over 16 years. His clinical course and histopathological features demonstrated the gradual changes from an early nonspecific skin lesion to a typical lesion of GSS, eventually leading to GSS concurrent with MF. At the initial stage, there were tuberculous granulomatous features suggestive of borderline leprosy despite its atypical clinical manifestation. In contrast,

the latest ones showed unique granulomatous changes associated with scattered large foreign body giant cells showing phagocytosis of lymphocytes and fragmented elastic fibers, and lymphocytic epidermotropism with the formation of a Pautrier's microabscesses in the overlying epidermis. During these changes of his clinical course from initial non-specific lesion to the latest MF stage IA (T1 N0 M0 B0) and then stage II B (T3 N0 M0 B0), his skin lesions partially responded to WHO anti-leprosy regimen and several courses of chemotherapy i.e. a combination of COP and MTX, and CHOP regimen.

Key words: granulomatous slack skin, leprosy, mycosis fungoides, chemotherapy

บทคัดย่อ :

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ผู้ป่วยชายไทย อายุ 57 ปี มีอาการผื่นนูนเรื้อรัง ไม่คัน บริเวณแขน ไหล่และรักแร้ด้านขวา ร่วมกับอาการผิวหนังแห้ง ผลพยาธิวิทยาพบเป็นแกรนูโลมาชนิด tuberculoid ผู้ป่วยได้รับการวินิจฉัยเป็นโรคเรื้อนระยะ borderline และได้รับการรักษาตามแนวการรักษาของ WHO ช่วงแรกตอบสนองต่อการรักษาบ้างต่อมาผื่นลุกลามมากขึ้น บางตำแหน่งแตกออกเป็นแผล ร่วมกับผิวหนังบริเวณรักแร้ขวาเกิดการห้อยย้อย ผลพยาธิวิทยาพบแกรนูโลมา ร่วมกับ foreign body giant cell ขนาดใหญ่จำนวนมาก ในชั้นดีพลาสซึมของเซลล์เหล่านี้พบเม็ดเลือดขาวชนิดลิมโฟไซต์ และเศษชิ้นส่วนที่แตกหักของเส้นใยอีลาสติกรวมอยู่ด้วย นอกจากนั้นยังพบเซลล์ลิมโฟไซต์ที่ผิดปกติรวมตัวกันเป็น Pautrier's microabscess แทรกอยู่ในชั้นหนังกำพร้า ผู้ป่วยได้รับการวินิจฉัยเป็น Granulomatous slack skin syndrome ร่วมกับ Mycosis fungoides stage IIB(T₃N₀M₀B₀) และได้รับการรักษาด้วยยาเคมีบำบัดหลายครั้งและหลายตำรับ เช่น COP ร่วมกับ MTX และ CHOP เป็นต้น

คำสำคัญ: granulomatous slack skin, โรคเรื้อน, mycosis fungoides, เคมีบำบัด

Introduction

Granulomatous slack skin (GSS) is a rare and indolent subtype of mycosis fungoides (MF)¹. This entity clinically presents with erythematous patches in the flexural portions, which gradually transforms into the peculiar bulky, pendulous areas of skin. Histologically, there is an elastolytic granulomatous infiltration, with atypical lymphoid cells, and occasional epidermotropism^{2,3}. The elastolysis produces a distinctive skin sagging appearance, whereas an abnormal, monomorphous T-helper cell immunophenotype with clonal rearrangement of the T-cell receptor beta and gamma gene has been demonstrated in the skin lesion⁴⁻⁷. Thus, GSS is often associated with preceding or subsequent lymphoproliferative malignancies such as mycosis fungoides, Hodgkin's disease, non-Hodgkin's lymphoma, primary CD30+ CTCL and histiocytosis X^{3,8}. However, in its early stage, some GSS cases were reported to be confused with leprosy^{9,10}, particularly in its endemic areas. In this paper, we report a middle-aged Thai male patient who had been initially misdiagnosed as having borderline leprosy, but after a long period of time eventually being confirmed as having GSS and MF that was partially controlled by chemotherapy.

Case Report

A 57-year-old Thai male presented with a 3-year history of slowly progressive, non-itchy, dry scaly, flesh-colored coalesced papules and macules on the

right forearm and right upper arm that gradually extended over the shoulder and axilla to produce an ulcerative lesion. Physical examinations which were retrieved from the patient's file revealed questionable clinical signs of either right ulnar nerve enlargement or cutaneous sensation loss at the lesional skin. Skin slit smear (SSS) was negative for *Mycobacterium lepra*. The first skin biopsy specimen obtained from the right forearm revealed tuberculous granulomatous changes consisting of epithelioid cells, Langhans type giant cells, and foam cells in the upper and mid-dermis with obvious grenz zone beneath the epidermis. Nerve bundles were well preserved. However, Fite Faraco staining for *M. leprae* done on the biopsy specimen was negative. Since histologic changes were only suggestive of borderline leprosy, he was placed under the treatment with WHO anti-leprosy regimen for paucibacillary case (PB case) and later he was registered to a leprosy clinic where the author (Dr. WP) first saw him. After 7 months, clofazimine (300 mg monthly and 50 mg daily) was added to the treatment, because of the lack of improvement. Moreover, prednisone (0.5 mg/kg) was periodically given for a few weeks as a reversal lepra reaction was suspected. Drastically, the skin lesions began to improve within 3 months, leaving only dry, scaly, slightly atrophic patches on the right upper arm and a slightly hyperpigmented patch at the right forearm. Hence, a 2-year-WHO anti-leprosy regimen for multibacillary cases (MB) was continued till the 19th month. Afterwards, he was lost to follow-up for 3

years and a half, because he believed that his skin condition was cured.

Thereafter, he sought medical treatment again because of recurrence of the skin lesions. On this visit, sensation loss at the lesional area was still questionable. The second histopathological study revealed extension of the granulomatous inflammation with more giant cell proliferation than those of the first skin biopsy, i.e. there was a heavy histiocytic infiltration intermingled with foam cells and many multinucleated giant cells in the whole dermis. Again, neither SSS or biopsy specimens could demonstrate *M. lepre*. PCR for *M. lepre* could not be done because it was not available in Thailand at that time. Under a diagnosis of relapsing borderline tuberculoid leprosy, he was treated again with anti-leprosy regimen for MB cases. At the completion of the 2-year-course his skin lesions showed only an ichthyotic appearance at the initial sites and skin sensation was intact. However, during post-treatment surveillance a few ulcers developed on his right buttock, off and on for a certain period of time, and responded well to antibiotic therapy. His general health remained well without any fever, night sweat or weight loss except for diabetes mellitus and hyperuricemia, both of which were well controlled.

At the 12th year of his clinical course, the previously affected skin lesion exacerbated again with the development of a new ulcer on the right buttock and the author re-evaluated his skin condition. On physical examination the previously subsided ichthyotic skin

lesions that involved about 6% of the body surface showed nodular inflammatory infiltration. There was a pendulous hanging mass on the right upper arm (Figure 1). In addition, purulent ulcers were noted in the center of the infiltrative scaly plaque on the right buttock (Figure2). Bacterial culture from the ulcerative lesion was positive for *Pseudomonas aeruginosa*. The third skin biopsy specimen obtained from the right shoulder revealed foci of lymphocyte epidermotropism and Pautrier's microabscesses in the epidermis (Figure3). Moreover, there were well-circumscribed granulomatous changes extending from the upper dermis into the subcutis. The infiltration composed of epithelioid cells with scattered extraordinary large foreign body giant cells with a large number of nuclei were seen, some of which were phagocytizing fragmented nuclei (Figure4).



Figure 1 Skin lesion on right shoulder: a mild scaly erythematous nodular plaque and a large sagging skin with firm lobulated nodular infiltration in suspending area.



Figure 2 Ulcerated lesions on right buttock.

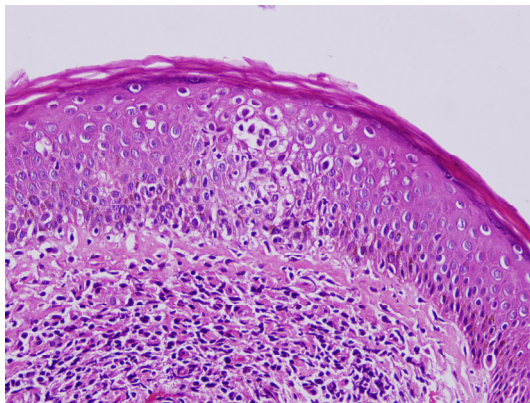


Figure 3 Epidermis showing lymphocytes epidermotropism and the aforementioned of Pautrier's microabscess (H&E, 200x).

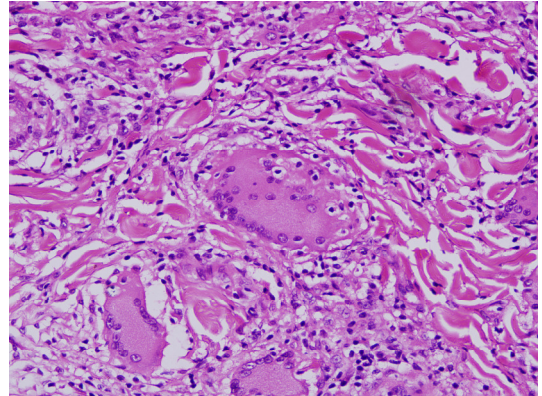


Figure 4 Large multinucleated giant cells showing phagocytosis of lymphocytes (emperipolesis) (H&E, 200x).

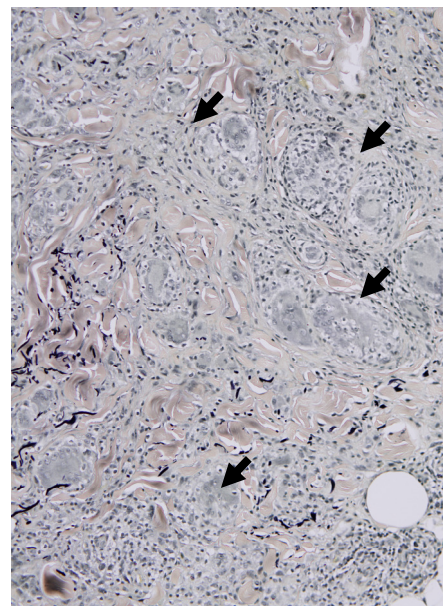


Figure 5a Diminished number of elastic fibers in infiltrative area, indicated by arrows, some elastic fibers that left were seen scatter in some area. (Verhoeff -van Gieson, 100x).

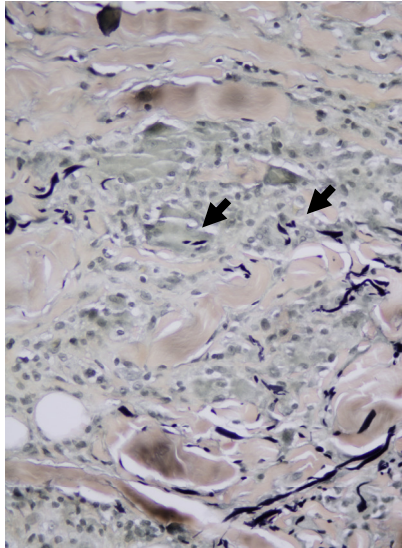


Figure 5b Fragmented elastic fibers inside of giant cells, indicated by arrows (Verhoeff -van Gieson, 400x).

Immunohistochemically, S-100 positive cells were present at the basal layer of the epidermis and around multinucleated giant cells. There were many T-cell marker-positive cells but only a few B-cell marker-positive cells in the granulomatous foci. The lymphocytic infiltration was composed of CD45Ro positive CD4 and CD8 positive cells. They were negative for CD 20, CD30, or factor XIIIa. Numerous CD 68 positive cells were present in the granulomatous areas. Verhoeff van Geison staining revealed a diminished number of elastic fibers in the lesional skin (Figure 5a) as compared to his normal skin (Figure 5b) and the presence of fragmented fibers in many giant cells (Figure 5c). Immunological studies on the peripheral blood showed that there were 2-3% Sezary

cells. CD4 and CD8 positive cells constituted 35% (553 cells cell/mm³), and 25% (394 cell/ mm³), respectively, with a 1.4 CD4/CD8 ratio. Immunoglobulin levels were slightly elevated with IgG 17.0 g/L and IgA 3.85 g/L. Multi-skin test was positive for tetanus. Neither T-cell receptor gene analysis of the peripheral blood mononuclear cells or the skin tissues or HTLV-1 serology was studied because such laboratory techniques were not available in Thailand at the time. so was CAT scan due to the patient's financial constraint. His general condition and extracutaneous involvement, which were evaluated by the blood profiles, chest x-ray, electrocardiogram, ultrasound, and bone marrow study revealed no visceral involvement. Only ultrasound study of the upper abdomen showed a mildly increased parenchymal echo in the liver, which could be due to chronic parenchymatous disease such as fatty liver. There was no subcutaneous lymphadenopathy to perform histological examination. These findings were suggestive of MF (CTCL) stage IA (T1 N0 M0 B0).¹¹

The ulcer on the buttock regressed with intravenous ceftriazone 2 g daily for a week that was followed by oral ciprofloxacin 500 mg twice daily for two weeks. The skin lesion was treated with re-PUVA (23 dosages with a total 193.7 joules/cm²). With this treatment, the fourth skin biopsy from the right shoulder revealed partial improvement, whereas those on the right buttock showed a minimal change, although histopathologically the latter revealed a decrease in both lymphocyte epidermotropism and cellular density. Shortly after that,

the former lesion on the right buttock began to ulcerate again but we could not increase Re-PUVA dosage because of its side effect consisting of a scaly erythrodermic change affecting all over the body. At this point we graded his skin condition as MF (CTCL) stage II B (T3 N0 M0 B0)¹¹. Because electron beam was not available at that time, we placed him under chemotherapy consisting of vincristine, cyclophosphamide and prednisone (COP) regimen, to which, however, the skin lesions showed a minimal response. Therefore, COP and methotrexate (CMOP) regimen was started from the second through the sixth course, to which all the skin lesions improved dramatically without any accompanying systemic adverse effect. Thereafter, he has remained in a well controlled state.

Two years later his skin lesion reactivated and extended beyond the initial site of involvement and new lesions appeared on the left forearm and left buttock, area of involvement was totally about 20% of the body. The fifth skin biopsy from the right shoulder showed Pautrier's microabscess and active giant cells phagocytizing fragmented elastic fibers so he was treated again with 8 courses of vincristine, cyclophosphamide, doxorubicin and prednisone (CHOP) regimen. Now he has been under follow-up schedule for two years and he is in a good state.

Discussion

The present patient exhibited such a long, obscure clinicopathological features which eventually changed

into typical granulomatous slack skin syndrome (GSS) whose latest lesion was concurrent with that of mycosis fungoides (MF). Namely, the latest changes are characterized clinically by the unique sagging of skin at the right axilla and histologically by the typical lymphocytic epidermotropism and Pautrier's microabscess. At the beginning, however, both of his clinical and histopathological findings rather mimicked those of borderline leprosy in this endemic region.

The histopathological differential diagnosis of GSS should include cutis laxa, anetoderma, mid dermal elastolysis, granulomatous mycosis fungoides and leprosy¹²⁻¹⁶. All of them showed a decrease of elastic fiber in the skin lesion, while only granulomatous MF and leprosy showed a granulomatous infiltration. Unfortunately, the reduction of elastic fibers was also a constant finding in leprosy lesion with a resultant clinical feature of sagging and wrinkles as well^{17,18}. However, leprosy patients develop minimal sagging and wrinkles on the face in particular due to the additive effect of UV lights^{3,17} whereas GSS mostly develops sagging on the flexural folds³. Thus, elastic staining does not seem to be of much help in distinguishing between GSS and leprosy at its early stage.

In the cases of GSS eventually there develops the unique features as observed in our present case. This patient was refractory to the treatment and being superimposed by repeated bacterial infections 12 years later. Moreover, the histopathologic examination demonstrated decreased elastic fibers and many

multinucleated giant cells with active phagocytosis and later there appeared epidermotrophism together with Pautrier's microabscesses. In its advanced stage, the clinical and histological features of GSS are so typical that the differential diagnosis is usually limited to a granulomatous variant of MF³. This case also supports the coexistence of GSS and other preexisting or subsequent lymphoproliferative diseases, which is noted in about 50% of the cases warranting a life-long follow-up¹².

Although, GSS itself does not seem to be life threatening, there was no radically effective treatment for this entity, except two cases which were claimed to have reached to complete remission after a few years of follow up^{12,19}. In most cases, various therapeutic modalities, e.g. clofazimine, steroids, etretinate, PUVA, chemotherapy, immunotherapy, radiotherapy, surgery or their combinations have been employed without lifelong complete remission^{8, 20-22}.

The initial lesions of the present case showed a good response to the anti-leprosy WHO regimen plus periodical administration of prednisone. However, they became gradually refractory. These medications themselves have an anti-inflammatory effect and clofazimine has been proven effective for several granulomatous skin lesions²³⁻²⁸. Based on these data, we think that clofazimine might have been at least partially effective for the early lesion of this case. There is no doubt that prednisone was also effective. Likewise, the disease was at least partially controlled by Re-PUVA

and chemotherapy consisting of COP and methotrexate, and lastly with CHOP regimen. According to his indolent course, we do not know for sure that his condition could be cured, thus, periodic multiple skin biopsies are planned for a long-term follow up.

In conclusion, we report here a typical case of GSS that showed a long-termed evolution of clinical course. The case warns us to be aware of the clinical and histopathological resemblance between GSS in its early stage and leprosy. It also displayed the validity of either clinical or histological findings of peripheral nerve involvements in distinguishing between the GSS and leprosy especially in a place where a highly sophisticated laboratory investigations such PCR for *M. leprae* and T-cell receptor gene analysis are not available.

Conflict of interest: NONE

Note: the short manuscript of this report case was published in the Journal European Academy of Dermatology and Venereology 2009;19(1):88-9 which unfortunately was not sufficiently long enough to tell the interesting natural course of this unique patient. The authors aim to publish the whole lengthy history of this case in the Thai journal of Dermatology because the case in detail will be of benefit to Thai dermatologists who must face with leprosy cases on daily basis.

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