Case Report

Granulomatous Mycosis Fungoides with Large Cell Transformation Misdiagnosed as Leprosy

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Background: *Granulomatous mycosis fungoides is an unusual histopathological variant of cutaneous T-cell lymphoma without clinical distinction from classic mycosis fungoides. Symptoms associated with peripheral nerve involvement have rarely been reported in the literature.*
Case Report: *The authors described a case of granulomatous MF stage IIB with large cell transformation who initially presented with leprosy-like condition and chronic left peroneal neuropathy. The patient received six courses of gemcitabine with greater than 90% improvement of skin lesions. The rest of the lesions were successfully treated with local electron beam radiation.*
Conclusion: *Granulomatous MF with neuropathy can be clinically misdiagnosed if there is no histopathological and immunohistochemical finding to support the diagnosis of lymphoma.*

Keywords: *Granulomatous mycosis fungoides, Large cell transformation, Granuloma annulare-like, Leprosy*

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Cutaneous T-cell lymphomas (CTCL) are primary T-cell non-Hodgkin lymphoma of the skin that are responsible for 75-80% of primary cutaneous lymphoma[1]. The World Health Organization classification 2008 and WHO/EORCT cutaneous lymphoma 2005 classified mycosis fungoides (MF) as T-cell neoplasm[1,2]. MF is the most common type of CTCL, which is found in almost 50% of all primary cutaneous lymphoma[1,2]. MF usually presents as a slowly progressive lesion that grows over the years or even decades, from patch to plaque and then tumor stage. Involvement of lymph node and viscera can occur in the later stage of the disease[3].

Granulomatous MF is a rare subtype of MF that have distinct histopathological features. However, it has no specific clinical characteristics when compared with classic pattern, as reported by Ackerman and Flaxman[4-9]. In most cases, the diagnosis was made solely on histological finding of granulomatous reaction associated with malignant lymphocytic infiltration[5,10]. The natural courses of granulomatous MF vary from indolent one to highly aggressive forms. Many reports suggested that granulomatous MF is not a benign variant of MF but an aggressive variant with early extracutaneous involvement[6,7,11-14].

The authors reported a case of granulomatous MF with large cell transformation that rapidly progressed to a tumor stage and clinically mimics leprosy.

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Case Report

A 52-year-old man presented with a 2-week history of solitary ulcerated nodule with rapid growth on the right nasolabial fold and a few erythematous plaques on the face for one month, predominantly on the forehead, and erythematous scaly patches on the trunk and the extremities for two years. He had also complained of progressive numbness of the left leg with left foot drop for seven years without history of trauma.

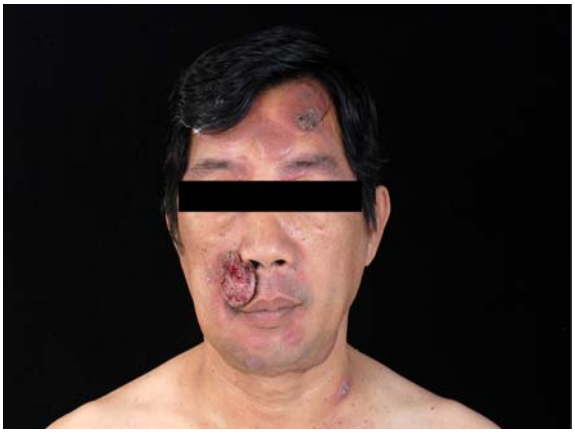

Fig. 1 A rapidly progressive, ulcerated nodule at right nasolabial area with multiple indurated erythematous plaques on the face and neck

One year ago, he was diagnosed with tuberculoid leprosy. At that time, slit-skin smear taken from both earlobes and the erythematous scaly patch on the left leg were negative for acid-fast bacilli. He was treated with oral rifampicin 600 mg monthly and dapsone 100 mg daily for six months without any improvement of the skin lesions.

A solitary, 2-cm diameter, erythematous ulcerated nodule on right nasolabial fold, with some erythematous plaques were noted on the face (Fig. 1) and multiple scaly, erythematous patches on the trunk and the extremities. The patient also had left foot drop. The motor power of the left tibialis anterior muscle and the extensor hallucis longus muscle was grade 0. There was sensory impairment along the distribution of the left common peroneal nerve. The magnetic resonance imaging (MRI) of the left leg showed fatty degeneration and atrophy of tibialis anterior muscle, extensor digitorum longus muscle, and peroneus longus muscle. No abnormality of left peroneal nerve was seen.

Skin biopsies were taken from the ulcerated nodule on the right nasolabial fold and an indurated plaque on the forehead. Histologically, the nodule (Fig. 2) showed superficial erosion with parakeratosis and pseudoepitheliomatous hyperplasia of the epidermis. There was diffuse infiltration by large, atypical pleomorphic lymphoid cells throughout the dermis with focal area of epidermotropism. The plaque lesion showed dermal infiltration by medium to large atypical lymphoid cells. Fifty percent of atypical lymphoid cells are composed of large cells. Epidermotropic atypical cells were detected and formed Pautrier's microabscesses. Moreover, there were palisading granulomas resembling granuloma annulare in the upper dermis. The granulomas were composed of histiocytes and multinucleated giant cells (Fig. 3). Acid-fast bacilli or fungi were not found. Immunohistochemistry demonstrated that the atypical lymphocytes were stained positively with antibodies to CD3, CD4, CD5 antigens, but they were not stained with antibodies to CD8, CD20, CD56, ALK, CD79a, and LMP1 antigens. Epstein-Barr virus encoded RNA in situ hybridization was negative. CD30 was negative in nodular lesion and scattered positive in the plaque lesion. T-cell receptor gamma gene demonstrated a monoclonal rearrangement in both lesions.

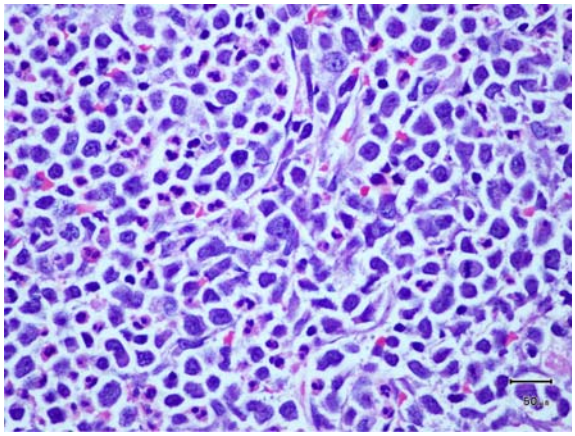

Fig. 2 The nodule at right nasolabial area; medium to large atypical lymphoid cells diffusely infiltrated in dermis (H&E x400)

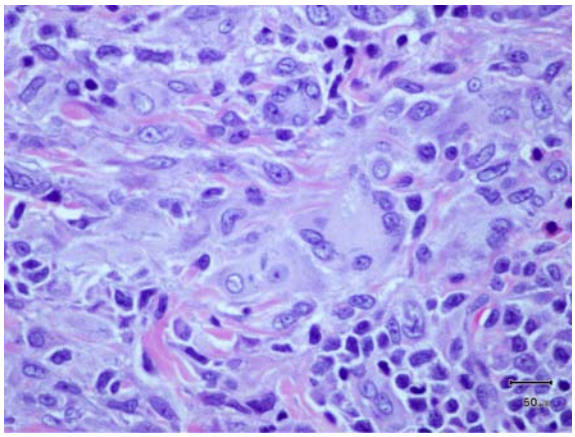

Fig. 3 The plaque at forehead; granulomatous reaction noted among atypical lymphoid cells (H&E x400)

The results of the following laboratory tests, complete blood count, renal and liver function test, lipids, serum urea and electrolytes, lactate dehydrogenase (LDH), and urinalysis were within normal limits. Human immunodeficiency virus (HIV), hepatitis B, and C virus serology were negative. Chest X-ray and computed tomographic scan of whole abdomen were normal. Bone marrow biopsy showed no abnormal findings and no Sezary cells were present in peripheral blood. Diagnosed stage IIB (T3N0M0B0) granulomatous MF (granuloma annulare-like variant) with large cell transformation was established.

Initially, the patient received six courses of intravenous gemcitabine on day 1, 8, and 15 of a 28-day cycle at dose of 1,200 mg/mm^2 of body surface area. The lesions resolved rapidly with greater than 50% reduction of the overall skin involvement after two courses of gemcitabine. After six courses, the response was greater than 90% improvement. There were remaining a solitary tumor on the left mandibular area and three infiltrative plaques on the right temporal area, left forearm, and left elbow, which were treated with local electron beam irradiation. The remaining lesions responded well to the radiotherapy.

Discussion

The presence of granulomatous reaction has been reported in skin lesions of MF, Sezary syndrome, subcutaneous panniculitis-like T-cell lymphoma (SPTCL), and sporadically in other types of cutaneous lymphoma. Granulomatous variant is rare in mycosis fungoides, but has been well-documented as well as the other rare entity of granulomatous slack skin (GSS). Usually, the first signs of granulomatous MF are erythematous papules and plaques. Poikiloderma and acquired ichthyosis occur in the minority of the cases[4,6,13,15-18]. At present, histological finding is a key to the diagnosis of granulomatous MF due to lack of specific clinical finding or criteria. Microscopically, there are malignant lymphoid cells infiltrations associated with granulomatous inflammation[9]. Granulomatous reaction found in MF have been divided into several patterns[11,15,19-21]. Sarcoidal-like is the most common pattern followed by granuloma annulare-like and tuberculoid granuloma with central necrosis[22]. The granulomatous pattern found in the presented patient is granuloma annulare-like variant defined by the presence of histiocytes that are arranged in a palisading pattern around degenerative collagen. However, there were no differences in prognostic outcome when based on histological classification[12].

Granulomatous reaction may obscure the atypical lymphoid cells and lead to the diagnosis of granuloma annulare, tuberculosis, and other infectious granulomas especially when found early in the course of disease[7,10,11,13,14]. The points that differentiate granulomatous MF from other granulomas are finding of epidermotropism, atypical lymphoid cells, and fibrosis of papillary dermis[7,13]. Epidermotropism is an important histologic feature of MF[23]. Without the finding of epidermotropism or when the epidermis is not examined or there is extensive granulomatous reaction, it is likely that the diagnosis will be missed[13].

Granulomatous MF has the uncertain role in prognosis. Previous studies claim that granulomatous reactions may represent a protective response of the host immune system against tumor progression[6]. However, there are trends toward unfavorable prognosis related to granulomatous type[11,12,14,24]. Up to 40% of the patients with granulomatous MF die of their diseases and 50% of mortality occurred within five years from emergence of the skin lesions[12,24]. There is a report of a patient with small intestinal granulomatous MF that caused intestinal perforation and gastrointestinal bleeding[12]. There are also reports of thyroid, pulmonary, chest wall, and central nervous system (CNS) involvement in patients with granulomatous MF[7,11,24]. The CNS involvement is rare but can occur early in the disease course and is related to mortality[24]. Rare peripheral nerve involvement of MF caused by direct neoplastic T-cell infiltration, represented by fibrosis of endoneurium, degeneration of axon, and loss of myelinated fibers, or a non-infiltrative mechanism without nerve invasion[25,26]. There is only one report of a patient with granulomatous MF whose both sural nerve and gastrocnemius muscle were infiltrated by atypical lymphocytes with granulomatous inflammation[27]. In the presented patient, the physical examination suggested chronic peroneal neuropathy with atrophic change of left tibialis anterior muscle, left extensor digitorum longus muscle, and left peroneus longus muscle. Therefore, the clinical combination of cutaneous lesions and neuropathy could lead to the provisional diagnosis of leprosy in the beginning. According to MRI finding, there was no sign of nerve invasion by tumor or any compressive lesion. Unfortunately, the nerve biopsy was not performed due to the patient's refusal. The relationship of chronic peroneal neuropathy and granulomatous MF could not be elucidated in the presented case.

Large cell transformation (LCT) of MF has been reported to be 8-55%[3,28]. In tumor lesion, LCT is commonly found in 46-55% and increases with advanced-stage of disease[28,29]. LCT found in the early disease course (within 2 years from the diagnosis of MF), extracutaneous site LCT, and advanced-stage disease are associated with poorer survival[30]. According to a previous study, median survival was 23.5 months in patients with LCT and two years after diagnosis[29].

Staging systems for MF based on tumor, lymph node, and metastasis (TNM) system, first devised by Bunn and Lamberg in 1979 and later revised to include blood stage (TNMB staging), may range from overall stage I to IVB[31]. Prognostic factors such as older age (> 60 year), tumor lesion, advanced stage, lymphadenopathy, high LDH, transformed MF, and bone marrow invasion correlate with poorer survival[29].

The treatment of granulomatous MF is the same as the recommendation of the classic MF[27]. The treatment of choice for late stage disease (stage IIB, III, IVA, and IVB) is systemic chemotherapy, which include single-agent chemotherapy with oral methotrexate, chlorambucil and etoposide or intravenous fludarabine, gemcitabine, liposomal doxorubicin, and 2-deoxycoformycin or combination regimen such as CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisolone)[32].

The cytosine nucleoside analogue gemcitabine (2', 2'-difluorodeoxycytidine) is a novel treatment for various hematologic malignancies. Gemcitabine monotherapy is effective even in refractory MF and in untreated and pretreated cases when given at a dosage of 1,000-1,200 mg/mm^2 of body surface area on day 1, 8, and 15 of 28-day schedule[33-35]. The overall response rate is 75% and 22% with complete response[33]. There were reports of MF with LCT who responded well to single agent gemcitabine therapy[36]. The advantage of gemcitabine is minor toxicity and the outpatient treatment protocol. Thus, this makes it a first line therapy of MF[33,35]. The presented patient well-tolerated gemcitabine therapy for its modest toxicity profile and easy schedule of administration.

Conclusion

This unusual case of granulomatous MF presenting as leprosy with chronic peroneal neuropathy illustrates the difficulties for clinicians to make the diagnosis. Histopathological and immunohistochemical study showing granulomatous component with neoplastic transformed lymphocytic infiltrates could lead to the definite diagnosis of granulomatous MF (granuloma annulare-like variant) with large cell transformation. The patient received six courses of gemcitabine with greater than 90% improvement of the skin lesions. The rest of the lesions were successfully treated with local electron beam radiation. There has been no systemic involvement of the disease for the period of one-year follow-up.

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รายงานผู้ป่วย granulomatous mycosis fungoides ที่การตรวจทางพยาธิจุลทรรศน์พบการกลายของเซลล์มะเร็งลิมโฟซัยท์ไปเป็นเซลล์ตัวใหญ่ (large cell transformation) ซึ่งเคยได้รับการวินิจฉัยเบื้องต้นเป็นโรคเรื้อน

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***ภูมิหลัง**: ลิมโฟมาที่ผิวหนังชนิด granulomatous mycosis fungoides ถือเป็นลิมโฟมาชนิดทีเซลล์ที่พบไม่บ่อย โดยมีอาการแสดงเหมือนลิมโฟมาที่ผิวหนังชนิดทีเซลล์ทั่ว ๆ ไป แต่ต้องอาศัยการตรวจทางพยาธิจุลทรรศน์เพื่อการวินิจฉัยที่ถูกต้อง ที่ผ่านมายังไม่ค่อยมีรายงานการตรวจพบอาการของรอยโรคที่เส้นประสาทส่วนปลาย*

***รายงานผู้ป่วย**: คณะผู้นิพนธ์รายงานผู้ป่วยที่ได้รับการวินิจฉัยเป็นลิมโฟมาที่ผิวหนังชนิด granulomatous mycosis fungoides ระยะ IIB ที่มีอาการแสดงเริ่มแรกเป็นผื่นที่ผิวหนังคล้ายโรคเรื้อน ร่วมกับมีอาการเสื่อมของเส้นประสาทพีโรเนียวด้านซ้ายเรื้อรัง โดยการตรวจทางพยาธิจุลทรรศน์พบการกลายของเซลล์มะเร็งลิมโฟซัยท์ไปเป็นเซลล์ตัวใหญ่ (large cell transformation) ซึ่งตอบสนองต่อการรักษาด้วยยาเจมซิตาบีน (gemcitabine) ทางหลอดเลือดดำรวม 6 ชุด ทำให้รอยโรคบริเวณผิวหนังหายมากกว่า 90% ร่วมกับใช้การฉายแสงอิเล็กตรอนเฉพาะที่ในรอยโรคที่เหลือ*

***สรุป**: ลิมโฟมาที่ผิวหนังชนิด granulomatous mycosis fungoides ร่วมกับอาการของรอยโรคที่เส้นประสาท ควรยืนยันการวินิจฉัยโดยการตรวจทางพยาธิจุลทรรศน์และการตรวจทางอิมมูโนฮิสโตเคมีจากรอยโรค*