Case Report

Cutaneous Granuloma in Systemic Lymphoma: A Case Report in Thailand

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A 68-year-old woman presented with multiple erythematous infiltrative nodules and plaques on her face, trunk and extremities, 7 months after having complete remission from chemotherapy treatment of non-Hodgkin's lymphoma. Biopsy from the skin lesion showed tuberculoid granuloma without lymphoma. Special stains and culture were negative for micro-organism. Immunohistochemistry revealed polymorphic T and B cells infiltration without evidence of malignancy. The skin lesions subsided completely after corticosteroid treatment. Two months later, she developed brain involvement of lymphoma that responded well to radiation and chemotherapy.

Keywords: *Lymphoma, Skin, Tuberculoid granuloma*

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The development of noncaseating granulomas at sites where there is no histologic evidence of malignancy is a well-recognized phenomenon[1]. Patients with Hodgkin and non-Hodgkin's lymphomas are well known to develop noninfectious granulomas at the involved and uninvolved organs[2,3]. However, cutaneous involvement is rarely observed[4]. The authors describe a patient with non-Hodgkin's lymphoma who developed cutaneous non-caseating tuberculoid granuloma. To the best of our knowledge, cutaneous granulomatous reaction of systemic lymphoma has never been reported in Thailand.

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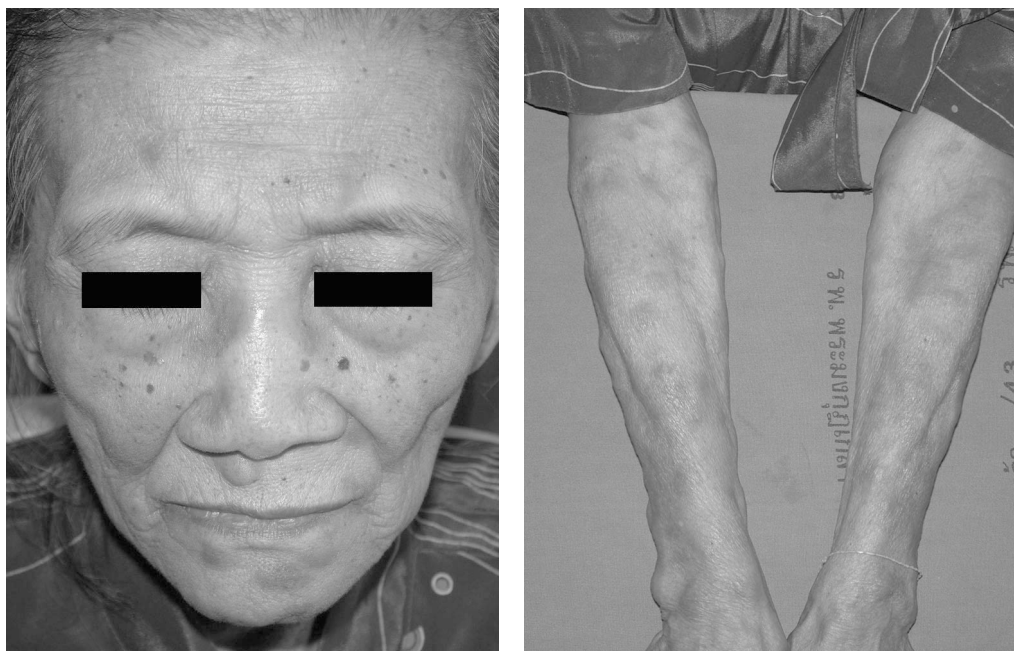
Case Report

A 68-year-old Thai woman presented with 1-week-history of fever, anorexia, weight loss, hepatosplenomegaly, leg edema, and generalized lymphadenopathy. Cervical lymph node biopsy revealed non-Hodgkin's lymphoma, large T cell type. Stage IV non-Hodgkin's lymphoma was diagnosed. She was treated with chemotherapy and was in complete remission after 1 year of treatment. Seven months later, she developed multiple erythematous infiltrative nodules and plaques on her face (Fig. 1a), trunk, and extremities (Fig. 1b) without lymphadenopathy and other systemic symptoms. Skin biopsy showed non-caseating tuberculoid granuloma involving the whole dermis (Fig. 2) without atypical cells (Fig. 3). Periodic acid Schiff and acid fast stains failed to reveal any



a b

Fig. 1 Multiple erythematous infiltrative nodules on the face (a) and foreams (b)

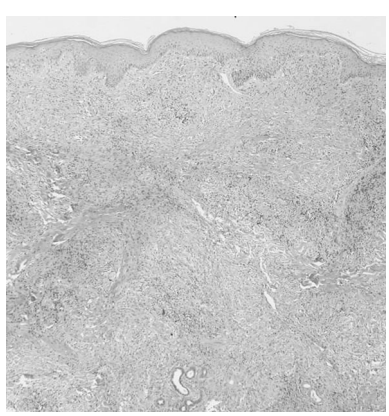


Fig. 2 Skin biopsy from the forearm showed nodular infiltration throughout the dermis. The infiltration was comprised of histiocytes and lymphocytes, forming non-caseating tuberculoid granuloma (X100 magnification)

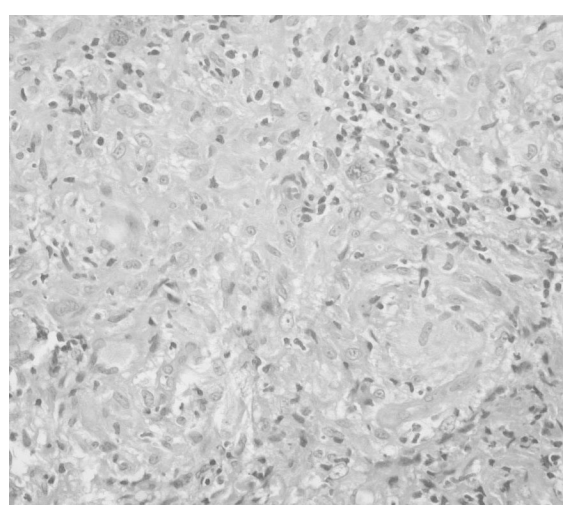


Fig. 3 Appearance of histiocytes, lymphocytes and giant cells in the granulomatous infiltration showed no atypical cell (X200 magnification)

microorganism. Immunohistochemistry revealed that the cellular infiltrations were positive for CD3, CD43, UCHL-1, CD20 and KPL-1, suggestive of polymorphic T and B-cells infiltration. Fungal and mycobacterial culture from the skin biopsy were negative. Investigations including complete blood count, bone marrow aspiration and biopsy together with computerized tomographic imaging were normal. She was diagnosed as cutaneous granulomatous reaction to systemic lymphoma and

was treated with oral prednisolone 30 milligrams per day. The skin lesions subsided completely within 4 weeks. Two months later, she developed right facial palsy. Magnetic resonance imaging of her brain did not reveal any abnormalities. However, malignant lymphoma with meningeal involvement was diagnosed. She was treated with whole brain radiation with intrathecal methotrexate and another course of chemotherapy. Her neurologic abnormalities recovered. Cutaneous granulomatous lesions recurred twice after that. Repeated skin biopsies showed the same histopathological findings. At present, she is doing well.

Discussion

Noninfectious granulomas can be found in both primary cutaneous and systemic lymphoma, either Hodgkin or non-Hodgkin's lymphoma[3,4,5]. Granulomatous infiltration (defined as a granulomatous reaction exceeding 25% of the dermal infiltrate) can be found in 1.8% of all cases of T-cell and B-cell lymphomas[6]. Cutaneous non-infectious granulomas can be classified into two types[7]. The first type is the specific cutaneous lymphoma that composes of neoplastic cells admixed with granulomatous infiltration. Granulomatous mycosis fungoides such as granulomatous slack skin is an example of this type[8]. Granulomas are often temporarily seen in the course of mycosis fungoides and may either precede or follow nongranulomatous mycosis fungoides[9]. This type of granuloma seems to be related to the presence of many T-lymphocytes within the infiltration[7]. They are prominent in T-cell lymphomas or in B-cell lymphomas with a strong T-cell reaction, such as marginal zone B-cell lymphoma[7]. Since the granulomatous inflammation may obscure the malignant component, diagnosis of lymphoma may easily be missed[6]. Investigations such as immunohistochemistry staining and T cell gene rearrangement are helpful in these cases.

The second type is the non-specific cutaneous granulomatous reaction to the underlying lymphoma characterized by non-caseating granulomas at sites free from any histologic evidence of malignancy[10]. The predominant sites of non-specific granulomatous reaction of lymphoma are lymph nodes, liver and spleen[3,10]. Skin is rarely involved[4]. Most of the reported granulomatous reactions are sarcoidal granulomas. However, other types of granulomas such as necrobiotic granulomas, granuloma annulare and tuberculoid granulomas have been described[5,11-13].

The present case developed cutaneous non-infectious noncaseating tuberculoid granuloma as a nonspecific manifestation of non-Hodgkin's lymphoma. Although histologic studies of granulomas are not enough to rule out a specific involvement of the skin by the neoplasm[5] and T-cell receptor gene rearrangement was not done, immunohistochemistry of the patient's biopsy showed polymorphic T and B-cell infiltration suggestive of immunologic response rather than neoplastic process.

Nonspecific granulomatous reaction can occur in precedent or after the underlying lymphoma. It can also occur during chemotherapy and radiotherapy[14]. The present patient's cutaneous granuloma preceded the recurrence of lymphoma. Even though the investigations including the magnetic resonance imaging and bone marrow biopsy were negative, the development of her neurological symptoms that were improved after radiation and chemotherapy suggested the reoccurrence of her lymphoma.

The pathogenesis of granulomatous reaction to systemic lymphoma is still unknown. It could be a peculiar immunological hypersensitivity reaction of the host against the tumor cells or persisting viral antigens[5]. The tumor cells may directly produce specific cytokines that cause granulomatous tissue response. The malignancy or chemotherapy

may prevent phagocytosis of immune complexes and/or other inciting agents causing granuloma[4,13,15]. The malignancy or chemotherapy may also predispose the host to unidentified opportunistic infection. There was a report of finding acid-fast coccoid forms in a patient with lymphoma and cutaneous sarcoidal lesions[16]. Furthermore, an evidence of HTLV-1 infection was found in one patient with sarcoidosis who later developed adult T-cell lymphoma/leukemia[4]. Lastly, the granulomas may be a response to the contrast media used in tumor staging[5].

The prognostic significance of cutaneous granulomatous reaction to lymphoma is still unknown. Some authors suggested that the granulomatous reaction to lymphoma is a host protective response that is a good prognostic factor[17]. However, many patients with granulomatous lymphoma had an aggressive clinical course[8,18].

Since cutaneous granulomatous reaction to systemic lymphoma is uncommon. Detailed history taking, careful physical examination and appropriated investigations should be done to exclude other more common causes of granuloma especially infection. Immunohistochemistry and T-cell receptor gene rearrangement should also be done to exclude lymphoma before making diagnosis of such a rare condition.

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Cutaneous Granuloma ในโรค Systemic Lymphoma: รายงานผู้ป่วย

กอบกุล อุณหโชค, ชสุรี สีตกะลิน, ไพบูลย์ ปุญญฤทธิ์

ผู้ป่วยหญิงไทยคู่ อายุ 68 ปี มีก้อนเนื้อสีแดงเกิดขึ้นที่ใบหน้า แขน ขา และลำตัว 7 เดือนหลังจากได้รับการรักษามะเร็งต่อมน้ำเหลืองชนิด non-Hodgkin จนอยู่ในภาวะโรคสงบ ผลการตรวจพยาธิวิทยาของชิ้นเนื้อจากก้อนเนื้อที่ผิวหนังดังกล่าวพบลักษณะของ tuberculoid granuloma โดยไม่พบเซลล์ของมะเร็งต่อมน้ำเหลือง การย้อมพิเศษและการเพาะเชื้อไม่พบเชื้อและลักษณะของเซลล์มะเร็ง ก้อนที่ผิวหนังของผู้ป่วยตอบสนองต่อการรักษาด้วยคอร์ติโคสเตียรอยด์ 2 เดือนต่อมาผู้ป่วยมีมะเร็งต่อมน้ำเหลืองเกิดขึ้นในระบบประสาททำให้มีอาการปากเบี้ยวและหนังตาข้างซ้ายตก ซึ่งตอบสนองดีต่อการรักษาด้วยการฉายรังสีและเคมีบำบัด