

Case Report

Extranodal NK/T Cell Lymphoma, Nasal Type, Presenting with Primary Cutaneous Lesion Mimicking Granulomatous Panniculitis: A Case Report and Review of Literature

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Background: Cutaneous extranodal NK/T-cell lymphoma, nasal type (NK/T) is relatively rare, associated with aggressive behavior and poor prognosis. Histopathological findings, immunohistochemical study, and EBV-encoded RNA (EBER) in situ hybridization are essential for the diagnosis.

Case Report: A 54-year-old Thai man with NK/T of the nasal cavity initially presented with cutaneous NK/T mimicking granulomatous panniculitis. The skin biopsies were performed twice due to the marked necrosis in the first one. The second biopsy revealed small, medium, and large atypical lymphoid cells infiltrating fat lobules with necrotic foci and granulomatous reaction. Within the granulomatous inflammation, the atypical lymphoid cells showing involvement of the blood vessel (angiocentricity) were noted. Immunostaining demonstrated that the atypical lymphoid cells marked with CD3, CD56, and TIA-1, but they did not mark with CD5, CD20, CD15, or CD 30. EBER in situ hybridization was positive.

Conclusion: Cutaneous NK/T can produce granulomatous panniculitis. The recognition of atypical lymphoid cells showing angiocentricity together with immunohistochemistry and EBER in situ hybridization are crucial for the correct diagnosis.

Keywords: Extranodal NK/T-cell lymphoma, Epstein Barr virus, Cutaneous lymphoma

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Extranodal NK/T cell lymphoma, nasal type (NK/T) is a rare type of lymphoma that usually has an aggressive clinical behavior. It commonly occurs in the upper aerodigestive tract, especially the nasal cavity. Other extranasal sites have been occasionally reported, for instance, skin, soft tissue, gastrointestinal tract and testis⁽¹⁾. Clinically, the patients with cutaneous involvement usually present with cutaneous nodules or plaques with systemic symptoms such as fever, malaise, weight loss and hemophagocytic syndrome⁽²⁾. Cutaneous involvement may present as a primary manifestation or emerge following the nasal cavity

lymphoma. Microscopically, atypical lymphoid cells, commonly various in size, diffusely infiltrate the dermis or subcutaneous tissue, producing necrosis due to the vascular infiltration (the so-called “angiocentricity”), a typical feature of this lymphoma. Immunophenotype of NK/T is characterized by reactivity of CD2, CD3 (cytoplasmic staining), CD56, perforin, TIA-1 and granzyme B. Demonstration of EBV genome in the lymphoma cells by in situ hybridization for EBV-encoded RNA (EBER) is necessary for diagnosis, but it may be skeptical in some cases⁽¹⁾.

The authors reported a case of NK/T who initially presented with cutaneous NK/T mimicking granulomatous panniculitis, then followed by the detection of a simultaneous nasal lesion. The authors reviewed the English literature, focusing on cutaneous manifestations, histopathologic patterns, immunohistochemical findings, and survival outcomes.

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Case Report

A 58-year-old Thai man initially presented with intermittent multiple oral ulcers for a year. Subsequently, he developed multiple erythematous plaques on his face and multiple poorly circumscribed, ulcerated, erythematous nodules and plaques on his arms, abdomen, and legs (Fig. 1). He also had low-grade fever for a month with 4-kg weight loss within two months. The first skin biopsy revealed lobular panniculitis with extensive necrosis and focal granulomatous reaction. Special stains for acid-fast bacilli and fungi were negative. The extensive necrosis prompted another skin biopsy. The second biopsy showed small, medium, and large-sized atypical lymphoid cells infiltrating subcutaneous fat lobules (Fig. 2A) together with scattered necrotic foci and granulomatous reaction (Fig. 2B). Eosinophilic infiltration with focal subcutaneous microabscesses was noted. However, among the granulomatous inflammation, large atypical cells were detected, showing angiocentricity (Fig. 2C). Immunohistochemical study demonstrated the atypical lymphoid cells marked with CD3 and CD56 (Fig. 2D and 2E), but they did not mark with CD4, CD5, CD8, CD20, CD15 or CD 30. TIA-1 and granzyme B were positive. In situ hybridization for EBER was positive (Fig. 2F). Based on these findings, NK/T was diagnosed. Investigation for staging of the disease showed intra-abdominal lymphadenopathy without bone marrow involvement. After receiving a course of CHOP regimen, he had high-grade fever that was treated by broad-spectrum antibiotics. Only sinusitis was found during the septic work up. Nasal biopsy for culture and pathologic examination was then performed. The nasal biopsy showed marked necrosis caused by lymphoma cells showing angiocentricity. The results of immunohistochemical study and EBER were identical to those found in the skin biopsy. In addition, polymerase chain reaction (PCR) for T-cell receptor (TCR) genes did not show any TCR gene rearrangement. Nasal tissue culture revealed growth of non-albicans *Candida*. Amphotericin B was subsequently administered without any clinical response. Finally, he died of septic shock, approximately three months after the diagnosis. No autopsy was performed.

Discussion

Although NK/T is commonly found in the nasal cavity, it can arise in extranasal regions. Chan et al reported that NK/T in extranasal sites was most common in the skin (14 out of 34 cases); the lesions could be either generalized or multiple in sites. Of the



Fig. 1 A subcutaneous nodule with epidermal ulceration at the abdomen

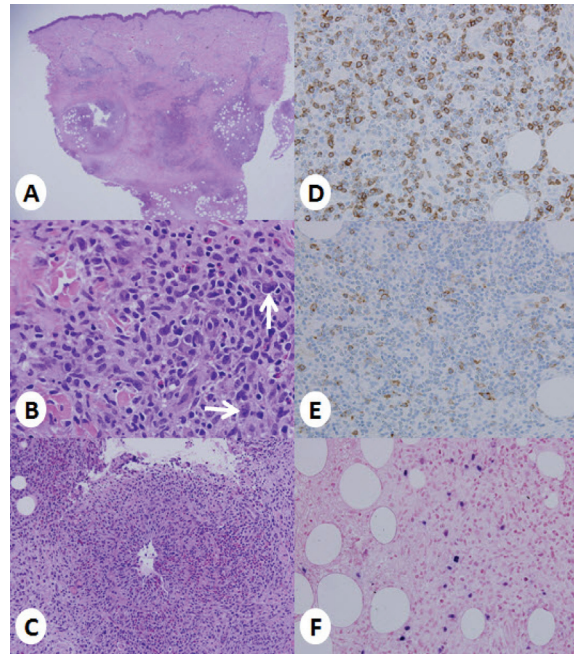


Fig. 2 (A) Skin biopsy shows lobular panniculitis (H&E x10). (B) Some atypical large lymphoid cells (white arrows) with prominent nucleoli are noted among granulomatous inflammation in subcutaneous fat (H&E x400). (C) Angiocentricity by atypical lymphoid cells is noted (H&E x20). (D) The atypical cells mark with CD3 (cytoplasmic staining). (E) CD56 (membrane staining). (F) Positivity of in situ hybridization for EBER

14 cases, three cases had other simultaneous organ involvement, including lung, lymph nodes and maxillary antrum⁽¹¹⁾. WHO/EORCT classification of cutaneous

Table 1. The literature review of NK/T with cutaneous involvement

	Case No. 1	Case No. 2	Case No. 3	Case No. 4	Case No. 5	The present case
Authors	Sandner et al ⁽³⁾	Miyamoto et al ⁽⁴⁾	Miyamoto et al ⁽⁴⁾	Miyamoto et al ⁽⁴⁾	Chang et al ⁽⁵⁾	Sithinamsuwan et al
Clinical information	Female 17 Multiple maculopapular patches	Female 69 7 x 4 cm ovoid dome-shaped tumor	Female 27 Erythematous plaques, some with annular-shaped lesion and bulla	Female 58 Erythematous lesion	Male 32 Discrete and confluent erythematous papule, patch and plaque	Male 58 Multiple poorly circumscribed, ulcerated, erythematous nodules and plaques
Location(s)	Trunk and both thighs	Parietal region of the scalp	Extremities	Trunk and extremities	Trunk and extremities	Face, trunk and extremities
Sequence of the lesions	Simultaneous skin and nasal involvement	Skin before nasal involvement 3 months	Skin before nasal involvement 11 months	Simultaneous skin and nasal involvement 16 months	Nasal before skin involvement	Simultaneous skin and nasal involvement
Other symptoms	Fever, peripheral lymphadenopathy, nasal swelling, and exophthalmos	Fever, nasal obstruction 3 months after the diagnosis	Nasal obstruction 7 months after the diagnosis	Concurrent fever and nasal obstruction	Nasal swelling with crusted ulceration	Intermittent multiple oral ulcers for a year
Hemophagocytic syndrome	+	N/A	N/A	N/A	N/A	-
Treatment(s)	No	RT and CMT	CMT	CMT	RT and CHOP	CHOP
Final outcomes	Died within a week after the diagnosis	Died within 11 months after the diagnosis	Died within 12 months after diagnosis	Clinical remission after the first course of CMT, and died at 3 months after the diagnosis	Died within 1 month after the cutaneous involvement	Died within 3 months after diagnosis
Histopathology of the skin lesion	Perivascular infiltration and epidermal necrosis	Dermal and subcutaneous infiltration	Dermal infiltration with bulla and necrotic keratinocytes	Perivascular infiltration	Patchy dermal infiltration	Atypical lymphoid cells infiltration in subcutaneous fat
Immunohistochemistry of the skin lesion	Angiocentricity Granuloma CD45RO CD3 CD4 CD8 CD56 TIA-1	+ N/A N/A - N/A N/A +	+ N/A - N/A N/A +	+ N/A + + N/A N/A +	+ N/A N/A + (cytoplasmic) N/A + +	+ + N/A + (cytoplasmic) - - + +
In situ hybridization for EBV PCR for TCR gene rearrangement	+	+	+	+	+	+
	N/A	No clonality	γ-rearrangement	N/A	No clonality	No clonality

N/A = not mentioned; RT = radiation therapy; CMT = chemotherapy

Table 2. The literature review of cases with primary cutaneous NK/T

	Case No. 1	Case No. 2	Case No. 3	Case No. 4	Case No. 5
Authors	Villaverde et al ⁽⁶⁾	Stokkermans-Duboid et al ⁽⁷⁾	Abe et al ⁽⁸⁾	Yamashita et al ⁽⁹⁾	Wanissorn et al ⁽¹⁰⁾
Clinical information	Sex Age Presentation(s) Location(s) Other symptoms Hemophagocytic syndrome Treatment(s) Final outcomes	Male 79 A 3 cm skin-colored nodule with small satellite lesions Leg Lymphedema N/A	Female 22 Annular erythema/indurated plaques Face, hip and bilateral legs N/A	Male 73 Erythematous induration Arm Axillary lymphadenopathy N/A	Female 40 Ulceration Thigh Facial palsy +
Histopathology of the skin lesion	Inguinal lymphadenopathy N/A CHOP Died within 4 months after the diagnosis Dense dermal infiltration by atypical cells with epidermotropism	Complete remission with the skin lesion Dermal infiltration by atypical lymphoid cells	CHOP Died within 2 months after the diagnosis Medium to large atypical lymphoid infiltration in subcutaneous fat N/A	IFN gamma Died within 2 months after the onset of the disease Skin necrosis with large atypical lymphoid infiltration in subcutaneous fat +	No Died within 5 months after onset of the disease Dense abnormal lymphoid infiltration in dermis and subcutaneous fat +
Immunohistochemistry of the skin lesion	Angiocentricity Granuloma CD45RO CD3	+ N/A N/A N/A + (cytoplasmic)	N/A N/A N/A +	N/A N/A + (cytoplasmic)	N/A N/A + (cytoplasmic and membranous) N/A - + N/A +
In situ hybridization for EBV PCR for TCR gene rearrangement	CD4 CD8 CD56 TIA-1 N/A N/A N/A	- - + + +	N/A N/A +	- - + +	N/A - + N/A +
		γ-rearrangement	N/A	N/A	No clonality

N/A = not mentioned; RT = radiation; CMT = chemotherapy; IFN = interferon

lymphomas has classified NK/T as an entity of mature T-cell and NK-cell neoplasms⁽¹²⁾, similar to the WHO classification (2008)⁽¹⁾. In our literature review (Table 1, 2), skin manifestations in NK/T are varied in patches, plaques, nodules, ulcer or even bulla. The lesion can be either solitary or multiple. Moreover, the skin lesions can arise before, after or concurrent with the nasal lesion. Histologically, infiltration of atypical lymphoid cells may be diffuse or patchy in the dermis or subcutaneous fat. Recognition of angiocentricity is an important point, which guides pathologists to the diagnosis of NK/T. In the present case, the authors found marked necrosis and granulomatous inflammation, but presence of infiltration by atypical lymphoid cells among the granuloma with angiocentricity raised the possibility of NK/T and eventually the confirmation of the diagnosis.

Granulomatous inflammation in cutaneous lymphoma has been reported. The granulomatous inflammation has mostly been found in mycosis fungoides and occasionally found in other cutaneous T-cell lymphomas, including granulomatous slack skin, CD30+ cutaneous T-cell lymphoma, subcutaneous panniculitis like T-cell lymphoma, adult T-cell leukemia lymphoma, small/medium pleomorphic T-cell lymphoma, peripheral T-cell lymphoma, unspecified and angioimmunoblastic lymphoma⁽¹³⁻¹⁷⁾. In addition, the articles of cutaneous B-cell lymphomas associated with granulomatous reaction, such as diffuse large B-cell lymphoma, follicular center lymphoma and primary cutaneous marginal zone B-cell lymphoma, have been published^(14,18). Interestingly, granulomatous reaction could occur in different patterns. Gallardo et al reported granulomatous patterns of cutaneous lymphoma with granulomatous component. They found 11 cases of sarcoidal-like pattern, two cases of granulomatous slack skin with mixture of sarcoidal-like pattern in one case, four cases of palisading granuloma with mixture of sarcoidal-like pattern in two cases and two cases of tuberculoid granuloma⁽¹³⁾. This implies that cutaneous lymphoma should be cautious in skin biopsy with obvious granulomatous reaction. Besides, recognition of atypical lymphoid cells and additional immunohistochemical study are helpful in the diagnosis of cutaneous lymphoma. However, infectious etiology should always be excluded firstly. Among nasal NK/T patients, granulomatous reaction has not been previously mentioned. There were some notifications of marked necrosis causing a difficulty in the diagnosis^(19,20). Furthermore, cutaneous NK/T associated with

granulomatous reaction had been mentioned⁽²⁾, but in our literature review (Table 1,2), granulomatous reaction has not been described in the cutaneous lesions of NK/T.

NK/T is considered as an aggressive lymphoma with poor prognosis. The present case died within three months after the diagnosis. In the literature review, majority of the patients with NK/T died within a short time, no longer than one year. An occurrence of complete remission was reported in only one patient⁽⁷⁾. Interestingly, a report of an indolent course with spontaneous regression of this lymphoma has been recently published⁽²¹⁾. Regarding the prognosis, NK/T with cutaneous involvement had poor prognosis⁽²²⁻²⁴⁾. Furthermore, associated extracutaneous involvement indicated poorer prognosis when compared with that of limited cutaneous form^(22,23). However, coexistence of CD30 and CD56 reactivity related to better response to chemotherapy among the patients with cutaneous involvement⁽²²⁾. In addition to nasal NK/T, cutaneous lesion might be associated with other extranasal NK/T cell lymphoma of other sites, for example, central nervous system and colon^(10,23,25). Thus, NK/T is an aggressive lymphoma that can have skin lesion either before or after those of the nasal or extranasal sites. Moreover, a concurrent association between the cutaneous lesions and lesions in the organs other than both of the skin and nasal cavity indicate poor prognosis.

Conclusion

NK/T is a rare type of cutaneous lymphomas. The cutaneous lesions may be primarily involved or may occur following lesions in the nasal or extranasal sites. Infiltration of atypical lymphoid cells with angiocentricity is a hallmark feature of this lymphoma. Even though granulomatous reaction has been seldom noted in NK/T, it can be found in many types of both B- and T-cell cutaneous lymphomas. Thus, in addition to infectious conditions, cutaneous lymphomas should be one of the differential diagnoses of granulomatous inflammation in a skin biopsy.

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Extranodal NK/T-cell lymphoma ที่มีรอยโรคผิวหนังคล้ายไขมันไต้ผิวหนังอักเสบแบบแกรนูโลมา: รายงานผู้ป่วย 1 ราย และการทบทวนวรรณกรรม

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ภูมิหลัง: Extranodal NK/T cell lymphoma, nasal type ของผิวหนังพบน้อย มีความรุนแรง และการพยากรณ์โรคไม่ดี ลักษณะตรวจพบทางพยาธิวิทยาที่สำคัญ และการตรวจโดยวิธีอิมมูโนฮิสโตเคมี รวมถึงการตรวจ *in situ hybridization* สำหรับเอ็มอาร์เอ็นเอของ Epstein-Barr virus (EBER) เป็นสิ่งที่จำเป็นในการวินิจฉัยโรคนี้

รายงานผู้ป่วย: ผู้ป่วยชายไทยอายุ 54 ปี เป็นมะเร็งต่อมน้ำเหลืองชนิด extranodal NK/T cell lymphoma, nasal type ที่โพรงจมูก แต่มีอาการเริ่มแรกทางผิวหนังซึ่งมีลักษณะพยาธิสภาพคล้ายชั้นไขมันไต้ผิวหนังอักเสบแบบแกรนูโลมา การตัดชิ้นเนื้อบริเวณรอยโรคของผิวหนังเพื่อให้ได้การวินิจฉัยจำเป็นต้องทำถึง 2 ครั้ง เพราะในครั้งแรกพบเนื้อตายเป็นบริเวณกว้าง ในครั้งที่สองจึงพบลิมโฟไซต์ผิดปกติทั้งขนาดเล็ก กลาง และใหญ่ แทรกอยู่ในชั้นไขมันไต้ผิวหนัง พบหย่อมเนื้อตายและแกรนูโลมาพร้อมด้วยลิมโฟไซต์ผิดปกติเหล่านี้ แทรกอยู่ในแกรนูโลมา ลูกกลมอยู่รอบหลอดเลือด เมื่อตรวจด้วยวิธีอิมมูโนฮิสโตเคมีพบวาลิมโฟไซต์ผิดปกติย้อมติด CD3, CD56 และ TIA-1 แต่ไม่ติด CD5, CD20, CD15 หรือ CD30 ส่วนการตรวจ EBER ได้ผลบวก

สรุป: Extranodal NK/T cell lymphoma, nasal type เมื่อเกิดในชั้นไขมันไต้ผิวหนังสามารถพบการอักเสบแบบแกรนูโลมาพร้อมด้วย การตรวจพบลิมโฟไซต์ผิดปกติที่ลูกกลมหลอดเลือด ร่วมกับการตรวจทางอิมมูโนฮิสโตเคมี และการตรวจ EBER มีความสำคัญในการวินิจฉัยโรคที่ถูกต้อง
