

Skin lesions as the first presentation in nodal follicular lymphoma: a case report.

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ABSTRACT :

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Follicular lymphoma is common subtype of indolent non-Hodgkin's lymphoma. The skin lesions as the first presentation in primary nodal follicular lymphoma are still unique and rarely first dermatological problem. Although, nodal follicular lymphoma has indolent course, metastasis to skin usually in the advance stage of occurring. The skin lesions should be differentiated from primary cutaneous follicular center lymphoma because of these two conditions have difference in clinical course, prognosis and treatment options. Immunohistochemical study of bcl-2 expression use to distinguish these two entities with a reference to each other. We report a case of 75 year-old woman firstly appears with only skin manifestation of multiple asymptomatic nodules on face, abdomen, back, and legs without other symptoms. The histopathology, immunohistochemistry and the CT scan of chest and abdomen were supported the diagnosis of nodal follicular lymphoma.

Key words: Follicular lymphoma, skin involvement, prognosis, treatment

บทคัดย่อ :

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สถาบันโรคผิวหนัง กรมการแพทย์ กระทรวงสาธารณสุข

โรคมะเร็งต่อมน้ำเหลืองชนิดฟอลลิคูลาเป็นมะเร็งระบบน้ำเหลืองชนิด non-Hodgkin's lymphoma การกระจายของโรคมะเร็งที่ผิวหนังพบได้น้อยมาก และมักบ่งบอกถึงการพยากรณ์ของโรคที่ไม่ดี อาการที่ผิวหนังมักมาด้วยตุ่มแดงได้

ผิวหนังบริเวณใบหน้า และลำคอ โดยต้องแยกโรคกับมะเร็งระบบน้ำเหลืองที่เกิดเริ่มต้นบริเวณผิวหนัง เนื่องจากการดำเนินโรค การพยากรณ์โรค และการรักษาแตกต่างกันมาก ซึ่งการแยกโรคจำเป็นต้องอาศัยการตรวจทางอิมมูโนพยาธิวิทยา เพื่อช่วยในการวินิจฉัย ในรายงานนี้ได้นำเสนอผู้ป่วยหญิงอายุ 75 ปีซึ่งมาโรงพยาบาลด้วยก้อนบริเวณผิวหนังหลายตำแหน่ง ซึ่งได้รับการวินิจฉัยว่าเป็น โรคมะเร็งต่อมน้ำเหลืองชนิดฟอลลิคูลาที่มีการกระจายของโรคมาที่ผิวหนังโดยอาศัยการตรวจทางพยาธิวิทยา อิมมูโนพยาธิวิทยา และการตรวจเอกซเรย์คอมพิวเตอร์เพื่อยืนยันการวินิจฉัย

คำสำคัญ: มะเร็งต่อมน้ำเหลืองชนิดฟอลลิคูลา, การพยากรณ์โรค, การรักษา

Introduction

Secondary cutaneous follicular lymphoma is an infrequent B-cell non-Hodgkin lymphoma that metastasis to skin, primarily affecting elderly woman with multiple non-tender erythematous nodules. Generally, it has a predilection sites for head and neck region.¹ We report here on a case of unique nodal follicular lymphoma presenting with multiple nodules on face, abdomen, back and legs in an elderly woman.

Case report

A 75 year-old woman was referred to Institute of Dermatology, Thailand with multiple asymptomatic erythematous nodules on her face, abdomen, back and legs for 2 years. The lesions firstly appeared on her left temporal area and gradually increase in size associated with other smaller nodules on right cheek, abdomen, back, and legs. She had other underlying disease of hypertension. She denied any associated fever, weight loss, and night sweats. She went to the local hospital and had been treated with topical medication. Unfortunately, there was no any clinical of improvement.

The physical examination revealed multiple, discrete, well-defined, indurate, erythematous, non-tender papules and nodules on face, trunk, and extremities. The largest lesion located on her left temporal area, approximately 3 cm diameters (Figure 1). There were no enlargements of cervical and inguinal lymph nodes. Other physical examination appeared normal. Blood count and liver function test were within normal limited. Serum LDH level was elevated at 467 mg/dl.

Histological examination from the left temporal area showed multiple closely packed nodules, resemble germinal centers but devoid of mantle zones, composed of atypical medium-sized lymphocytes with hyperchromatic nuclei and scant cytoplasm intermingled with large atypical lymphocytes that characterized by vesicular nuclei, prominent nucleoli and abundant cytoplasm, throughout the dermis (Figure 2A, 2B). Immunohistochemistry revealed that positive to CD20, CD79a, CD10, bcl-2, bcl-6, but the absence of CD3 (Figure 3).

Further investigations, computed tomographically (CT) chest found the enlargement of lymph node at

right pretracheal area size 13 mm, with slightly enlarged on the prebronchial and the aortopulmonary (AP) window. There were enlargement of mesenteric lymph nodes at the below left kidney pole level accompanies with 32-mm of inhomogeneous hypodense mass of right kidney and revealed splenic hypodense nodule size 8 mm from CT abdomen. The bone marrow biopsy showed the normal of 30% cellularity, and negative for malignancy cell. The abnormal cellular aggregation also was not found.

Pathological and immunohistochemical diagnosis suggested nodal follicular lymphoma with secondary skin involvement. Unfortunately, the patient refused chemotherapy and then finally her body was expired at 7 months after initial diagnosis.



Figure 1 Erythematous indurated nodule on left temporal area.

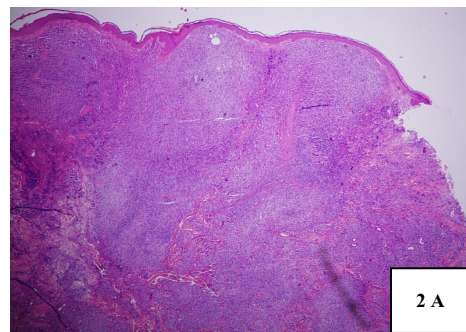
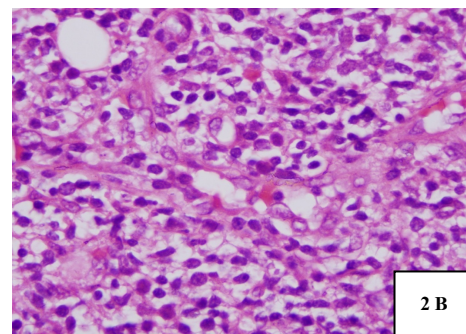


Figure 2 H&E. (A)(x4) Multiple closely packed nodules, resemble germinal centers but devoid of mantle zones. (B)(x100) Atypical neoplastic cells consist of centrocytes and centroblasts.

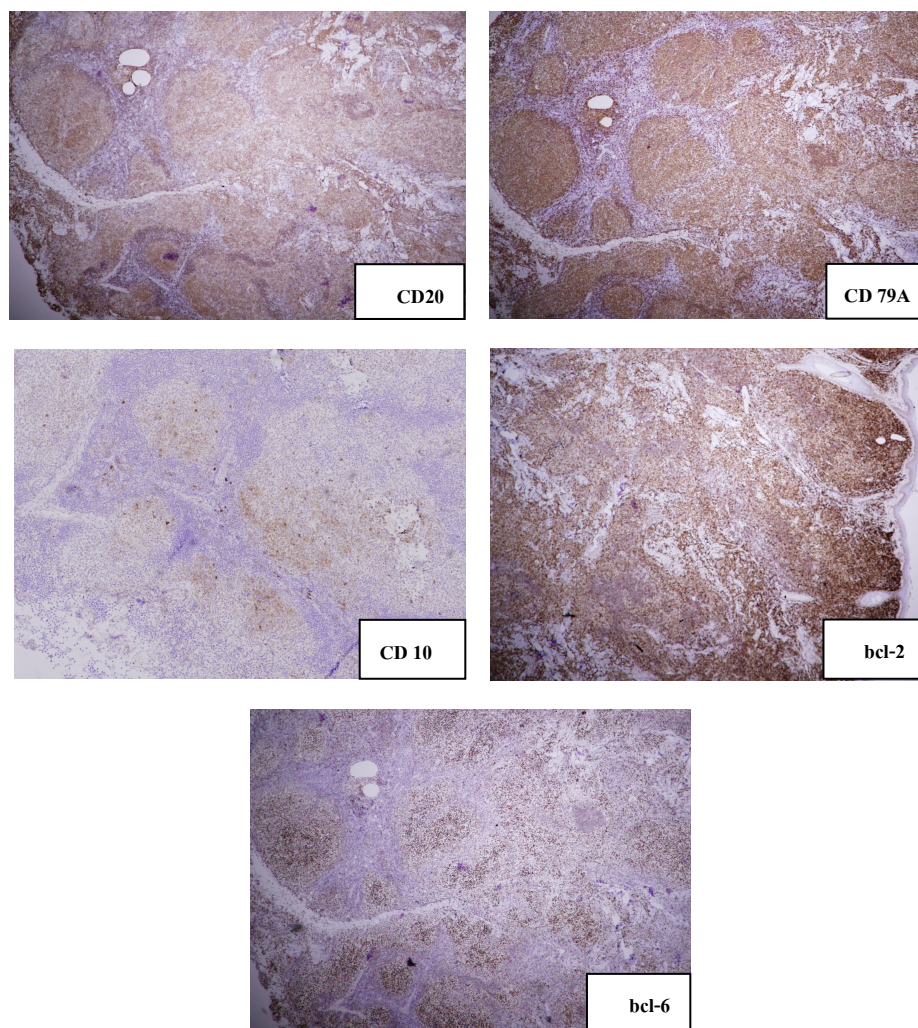


Figure 3 (x10). Positive CD20, CD79a, bcl-2, bcl-6, and CD10.

Discussion

The non-Hodgkin's lymphoma (NHL) is malignancy of B-cell or T-cell that usually developed from lymph node tissues.² Incidence rates of NHL are varies around the world. In Thailand, the incidence of NHL is limited case. In 2001 to 2003, the data of National cancer Institute from Thailand that was found the incidence rate of NHL account for about

5.4:100,000 person-years in male and 4.2:100,000 person-years in female,³ when compared with the data from United State which had higher incidence of NHL, account for 19.1:100,000 person-years.²

Follicular lymphoma (FL) is subtype of indolent B cell NHL that transformed follicular center B cells which usually occur in adulthood to elderly slightly female predominance patients with median age of onset

varies from about 51 to 63 year-old.^{4,5,6,7} However, the disease may be occurs in children and young patients under 15 year-old about 4%.² The incidence of FL is high in Europe countries and America account for 20% to 30 %^{4,8} compared with less frequency in Thailand that was found only about 3.8% to 9% of all NHL.^{9,10}

Clinical presentation of Follicular lymphoma usually present with long period of asymptomatic lymphadenopathy and about 70 % accompanies with bone marrow involvement.⁴ Splenomegaly is another common presentation of the disease.⁴ Constitutional symptoms, include fever, night sweat and weight loss are unusual, which can be occur less than 20%.⁴ Of all cases of FL, only about 3.8% to 4% show evidence of secondary skin involvement (secondary cutaneous follicular lymphoma, SCFL), that are characteristic of dissemination of the disease, which usually showed stage III or IV at presentation.^{1,6} Clinical of SCFL showed asymptomatic solitary or multiple erythematous papules or nodules on head, neck and trunk regions, that usually presents after the clinical of lymphadenopathy 3 to 7 years, but less frequency can occur at the same time of lymph nodes involvement.^{1,6}

Translocation that resulted from the fusion of bcl-2 oncogene on chromosome 18 with immunoglobulin heavy chain joint gene on chromosome 14 (t^{14; 18} translocation), initiated over expression of anti-apoptotic bcl-2 protein, are hallmark of diseases found approximately 70% to 85% of all FL patients.^{4,11-12}

The characteristic histopathology of FL shows neoplastic cells are arranged in closely pack nodule with devoid of metal zone. There are two types of neoplastic cells. The first, centrocytes are prominent cells that characterized as small to medium-sized lymphocyte with scant cytoplasm and sometimes have inconspicuous nuclei and angulated nuclear contour. The second, there are larger transformed lymphocytes with round to oval nuclei, vesicular chromatin and several visible nucleoli, which called as the centroblasts.¹³ Tumor cells tend to express the B-cell-associated markers, included CD20, CD19, CD22, and CD79a. Other immunohistochemical studies of the literature showed positive result to CD10, bcl-6 and bcl-2. Most cases of that are CD23 and CD5 negative.^{4,13}

Our patient developed asymptomatic cutaneous nodules on multiple sides of body with predominate on the face for 2 years without any other presenting signs, which is uncommon presentation of the disease. Although, the differential diagnosis included primary cutaneous lymphoma, lymphoma/leukemia cutis, lymphocytoma cutis, and lymphocytic infiltration of Jessner. The result of skin biopsy from left temporal area suggested follicular lymphoma. The immunohistochemical studies in our patient also confirmed the diagnosis of follicular lymphoma. Further diagnosis by CT scan, the lymph nodes on both sides of diaphragm and the splenic involvement had been found. Unfortunately, our patient refused further investigation for lymph node biopsy and t^{14; 18} translocation studies.

Table1 Distinguish between primary cutaneous follicular center lymphoma (PCFCL) and secondary cutaneous follicular lymphoma (SCFL, nodal follicular lymphoma)

	PCFCL	SCFL
Patients	Elderly	Elderly
Sex	Male> female	Slightly female predominant
Clinical:	Remain localized to skin	Lymph node, bone marrow, spleen,
	Very low tendency to extracutaneous spread	Skin involve only 4%
Lymphadenopathy	Rare	Present, asymptomatic lymphadenopathy for year
Cutaneous presentation	One / grouped of red to plum colored papules, plaques, nodules	Same
Common cutaneous location	Head, neck, trunk	Head, neck, trunk
Histology		
- Pattern	Nodular to diffuse pattern	Nodular to diffuse pattern
- Germinal center	Germinal center	Germinal center
- Mantle zone	No mantle zone	No mantle zone
- Centrocyte/Centroblast	Positive/positive	Positive/positive
Immunohistochemistries		
- CD 20	+	+
- bcl-2	-	+
- bcl-6	+	+
- CD 10	+	+
- CD 23	+/-	-
Prognosis	Good	Poor

Histologically, SCFL should be differentiated from primary cutaneous follicular center lymphoma (PCFCL) (Table1) that has better prognosis and tend to response well to treatment.¹ PCFCL is indolent, mostly skin limit condition which 5 years survival rate greater than 95%

to 98%.¹⁴ The cutaneous presentation and histopathology may be indistinguishable these two conditions. However, the bcl-2 expression helps to differentiate SCFL from PCFCL which only about 10% of the PCFCL patients are positive for bcl-2.^{11,13,14,15}

Further more the diagnosis of PCFCL should be consider when patient has cutaneous lesion without extracutaneous involvement at least 6 month from the first diagnosis.¹⁶ In our case although histological studies cannot distinguish between PCFCL and SCFL, the presentation of cutaneous involvement accompany with lymphadenopathy and bcl2 positive from the tissue section suggest diagnosis of SCFL.

Prognosis factor of FL based on independent risk factor, called follicular lymphoma international prognostic index or FLIPI, including hemoglobin < 12 g/dl, serum LDH > upper normal value, Ann Arbor stage III-IV, number of nodal sites > 4 and age > 60 years.^{4,17} The FLIPI use to dividing patients into groups (stages) including low risk (0–1 risk factor), intermediate risk (2 risk factors), and high risk (3 or more risk factors) which have difference survival rates.^{4,16} In our elderly patient, she had stage IV of Ann arbor staging (diffuse or disseminated involvement of one or more extralymphatic organs) and elevated LDH level, so she had high risk factor of FLIPI, which showed 5 and 10 years overall survival rates about 52% and 36%, consecutively.⁴ But she died earlier as 7 month after the first diagnosis.

In advanced stage III and IV, symptomatic patients are usually treated with rituximab combine with chemotherapy such as CHOP, CVP regimens or purine analog-based schemes. Adding of rituximab cause improvement of response rate and overall survival rate of FL. Newer agents, anti-CD80 monoclonal antibodies,

anti-CD20 monoclonal antibodies, IL-2 and B-cell kinase inhibitors are currently being studied.⁴

We report a rare case of nodal follicular lymphoma in elderly woman presented with only cutaneous sign at the first time of presentation. Histopathological and immunohistochemical studies compatible with SFCL. The diagnosis of SFCL is challenging and must be differentiated with PCFCL because of distinct clinical course and prognosis. Our patient denied the treatment with chemotherapy and she died at 7 month after diagnosis. Because of SFCL may be asymptomatic and has progressive course, so the diagnosis should be awareness in an elderly patient that presenting with multiple erythematous nodules even if no other clinical signs.

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