J Cutan Pathol 2009: 36 (Suppl. 1): 25–30
doi: 10.1111/j.1600-0560.2008.01203.x
Blackwell Munksgaard. Printed in Singapore

Journal of
Cutaneous Pathology

Cutaneous involvement in the lymphoepithelioid variant of peripheral T-cell lymphoma, unspecified (Lennert lymphoma). Report of a case and review of the literature

Lennert lymphoma (LL), or the lymphoepithelioid variant of peripheral T-cell lymphoma, is an uncommon entity with rarely seen or reported presentations in the skin. Cutaneous involvement of LL has been characterized by asymptomatic, non-ulcerated, red to violet papules, nodules and small plaques (less than 5 cm) on the trunk and extremities. Histologically, there are localized cellular lymphoid infiltrates in the dermis that tend to localize around blood vessels or skin appendages. Key to the diagnosis of LL is the presence of epithelioid histiocytes and atypical small lymphoid cells without increased vascularity or epidermotropism. Immunophenotyping shows a dense monoclonal T-cell population commonly associated with aberrant loss of T-cell-associated antigens. T-cell receptor gene rearrangements are also identified. Patients typically present with advanced stage and have a low 5-year survival. Herein, we present a case of cutaneous involvement by LL at the time of initial presentation that persisted after initiation of chemotherapy and was finally verified as secondary cutaneous involvement of LL 1 year later histologically, immunophenotypically and by T-cell receptor gene rearrangement studies.

Summers TA, Rush W, Aguilera N, Lupton G. Cutaneous involvement in the lymphoepithelioid variant of peripheral T-cell lymphoma, unspecified (Lennert lymphoma). Report of a case and review of the literature.

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Accepted for publication November 8, 2008

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Since first described in 1968 by Lennert and Mestdagh[1] as 'Hodgkin's disease with constantly high content of epithelioid cells', through convincing attempts at classification by Burke and Butler[2] and Kim et al.[3] as a distinct entity, and finally definitive establishment as a T-cell lymphoma by Feller et al.,[4] Lennert lymphoma (LL), also known as lymphoepithelioid lymphoma, has remained an ambiguous diagnosis that has been considered by some as purely a pathological description.[5] Currently, LL is classified in the WHO classification of lymphomas as 'lymphoepithelioid cell variant of the peripheral T-cell lymphomas, unspecified' because of insufficient evidence that it shows any specific clinical features.[6] It is an uncommon variant of peripheral T-cell lymphoma, and cutaneous involvement is rarely seen

or reported.[3,7–9] Herein, we present a case of LL with multiple sites of cutaneous involvement at initial presentation, which persisted after initial diagnosis and treatment, and that were histologically diagnosed as LL approximately 1 year post-induction of combination chemotherapy.

Case report

A 56-year-old man presented with fever, fatigue and weight loss accompanied by generalized lymphadenopathy. He was noted to have an erythematous macular eruption on his right shoulder and back, clinically expected to be lymphoma, along with multiple pigmented nodules, believed to be nevi, distributed diffusely across his back. His medical history was significant for melanoma of the prepuce, which was excised without evidence of relapse, and an unspecified granulomatous dermatitis. An abdominal and pelvic computed tomography scan showed an enlarged spleen with confirmation of enlarged cervical, axillary and inguinal lymph nodes that were identified clinically. Because of a high clinical suspicion for malignancy, an excisional biopsy of his right inguinal lymph node was performed and was diagnostic of peripheral T-cell lymphoma of the lymphoepithelioid variant (LL). He was subsequently scheduled for a bone marrow biopsy approximately 1 month later. At this time, he had no new complaints and was in no acute distress. However, his skin and nodal findings remained unchanged. His bone marrow analysis was unremarkable except for a small population of abnormal T-cells, identified by flow cytometry, consistent with minimal bone marrow involvement by the patient's T-cell lymphoma. Combination chemotherapy was initiated with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) and achieved remission for 11 months. Because of the persistence of his skin lesions posttreatment, the erythematous macular rash on his right shoulder was biopsied. Thirteen nevi were also excised. He was then treated with a new combination chemotherapy regimen consisting of carboplatin, etoposide and ifosfamide. He expired 3 months later from septic shock and respiratory failure, 14 months after initial diagnosis, after presenting with neutropenic fever, thrombocytopenia and anemia for which he refused bone marrow transplantation and desired only supportive care.

Materials and methods

We received his inguinal lymph node, a deep shave biopsy of his right shoulder, and three excised nevi for evaluation. All specimens were reviewed using routine light microscopy and phenotyping by immunohistochemistry. The phenotypic profile for the lymph node included CD7, CD3, CD5, CD30, CD8, CD25, CD23, CD21, CD4, CD20, CD2, CD163, CD1a, CD117, CD68 and CD45rb. Kappa and lambda *in situ* probes were also prepared. The immunophenotypic profile for all skin specimens included CD20, CD2, CD3, CD4, CD5, CD7, CD8, CD30 and CD56. Polymerase chain reaction (PCR) analysis of lymph nodal tissue and of skin was performed to assess for monoclonal gene rearrangements of T-cell receptor (TCR)-beta and of TCR-gamma. A search of the Armed Forces Institute of Pathology files back to 1970 revealed no further cases of cutaneous involvement by LL.

Results

Lymph node

The inguinal lymph node biopsy was provided for review. The lymph node architecture was completely effaced by a diffuse proliferation of small lymphocytes with irregular-appearing nuclei and numerous intermixed plump epithelioid histiocytes (Fig. 1A). Vascular proliferations were not observed nor were Reed-Sternberg cells. Diffuse immunoreactivity for these small lymphocytes was noted on CD2, CD4, CD5, CD8 and CD3 with decreased immunoreactivity for CD7 (Fig. 1B,C). Molecular studies via PCR showed biclonal gene rearrangements of TCR-gamma with two peaks at 65 and 97 base pairs (Fig. 3).

Skin

The shave biopsy obtained from the right shoulder showed multiple nodular aggregates of small lymphocytes and epithelioid histiocytes in the superficial dermis and abutting the epidermis, with scattered lymphocytes within the epidermis and vacuolar degeneration of the basal cell layer (Fig. 2A). Plasma cells and eosinophils were not identified. Rare multinucleated histiocytes were noted but well-formed granulomas were not present. Rare mitotic figures were observed in the lymphoid infiltrate. Vascular alterations and cellular infiltration of adnexal structures were not identified. Special stains for microorganisms were negative. Immunostains were performed and showed diffuse immunoreactivity for CD3, decreased reactivity for CD7 and scattered cells were reactive for CD20 (Fig. 2B,C). CD4-positive T lymphocytes predominated over CD8-positive lymphocytes.

Two of the 13 excised nevi were of particular interest because of their associated lymphohistiocytic infiltrates. The two nevi excisions of concern showed nearly identical features. Each showed an atypical 'dysplastic' junctional nevus along with

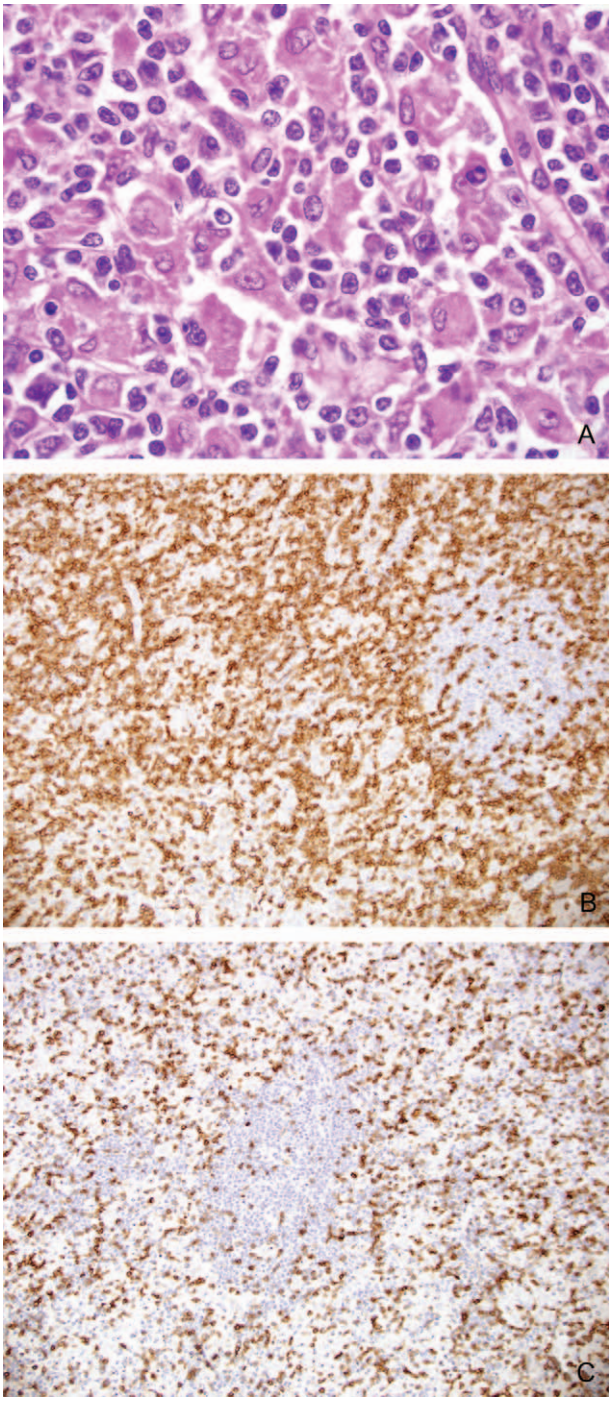

Fig. 1. A) Lymph node with proliferation of small atypical lymphoid cells and numerous small poorly defined clusters of epithelioid histiocytes. The lymphocytes display slight nuclear irregularities (lymph node hematoxylin and eosin ×400). Immunohistochemical stains for CD3 (B) and CD7(C) show loss of CD7 expression (lymph node Immuno histochemistry (IHC) ×100).

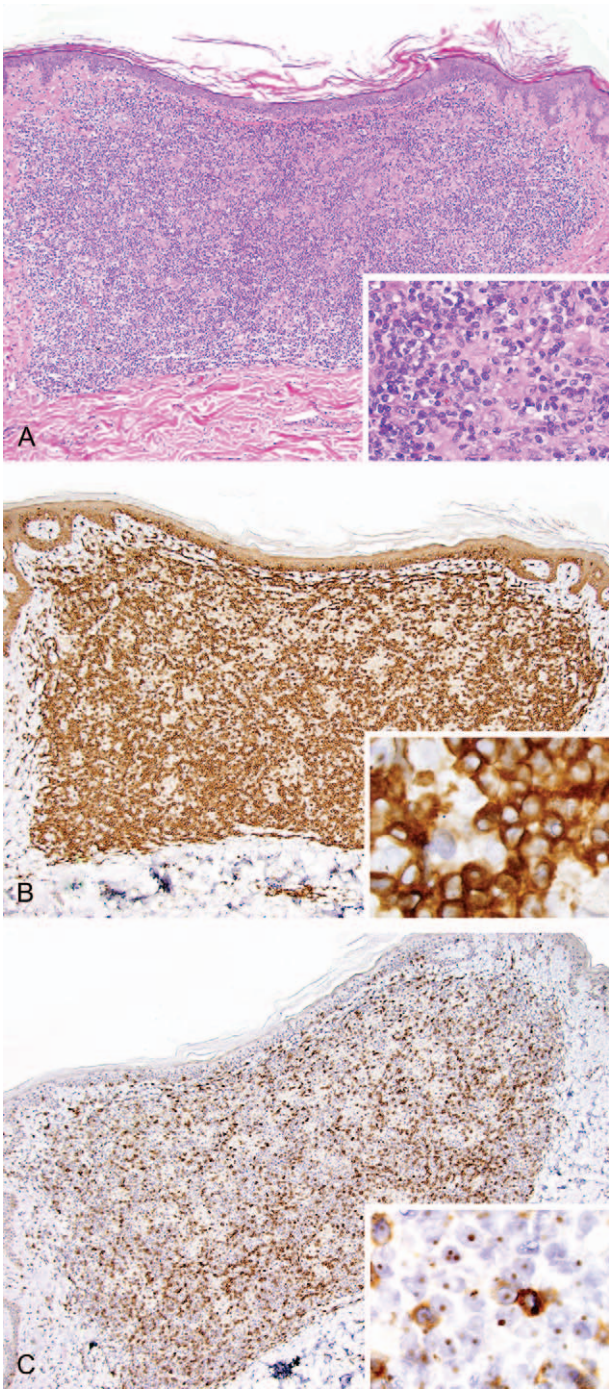

Fig. 2. A) A nodular aggregate of small lymphocytes and epithelioid histiocytes in the superficial dermis (skin H&E ×40). Inset shows similarity to lymph node specimen with slight nuclear irregularities of lymphocytes and presence of clusters of epithelioid histiocytes (skin H&E ×400). Immunohistochemical stains for CD3 (B) and CD7(C) show loss of CD7 expression, same as the lymph node (skin Immuno histochemistry (IHC) ×100). H&E, hematoxylin and eosin.

a nodular aggregate of small lymphocytes mixed with epithelioid histiocytes in the dermis. Vascular alterations and cellular infiltration of adnexal structures by the lymphocytes was not identified. Diffuse immunoreactivity was noted for CD3, decreased reactivity for CD7, and scattered cells were reactive for CD20. CD4-positive T lymphocytes predominated over CD8-positive lymphocytes.

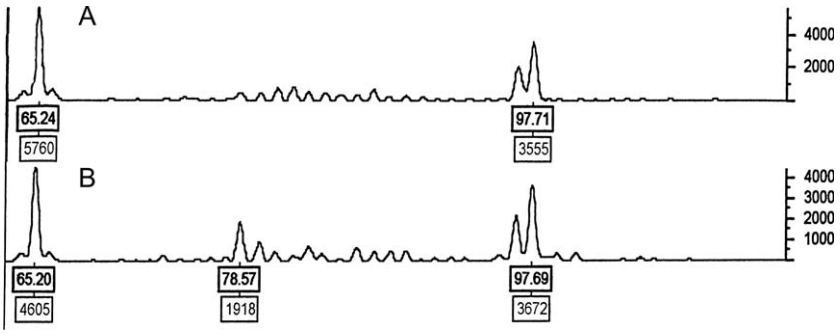

Fig. 3. Matching biclonal gene rearrangements of T-cell receptor (TCR)-gamma with matching dominant peaks at 65 and 97 base pairs between the lymph node (A) and the skin (B).

Molecular studies on selected skin specimens via PCR showed biclonal gene rearrangements of (TCR)-gamma with two peaks at 65 and 97 base pairs (Fig. 3).

Discussion

Cutaneous manifestations of LL are relatively infrequent. Non-specific findings such as infections,[10] prurigo nodularis[11] and atypical granuloma annulare[12] have been reported in association with LL. As uncommon as these reports are, even more so are reports of cutaneous involvement by LL. In the two large American series reviews of LL, only three of 34 patients were reported as having cutaneous involvement by LL at time of presentation, or developing involvement sometime after initial diagnosis.[2,3] A review of the literature, including the two previously mentioned series, reveals only nine reported cases of cutaneous involvement by LL.[3,7–9] Of these nine, seven cases had cutaneous involvement at the time of initial diagnosis and treatment.[3,8,9] Where clinically described, cutaneous involvement by LL has been characterized by asymptomatic, non-ulcerated, red to violet papules, nodules and small plaques (less than 5 cm) on the trunk and extremities.[3,7–9] In the case reported on by Kiesewetter et al.,[8] the patient's skin lesions responded to chemotherapy with resolution of some of them. To our knowledge, this is the first case reported of cutaneous involvement by LL at presentation with confirmation of the presence of malignant cells in the skin and lymph node by matching biclonal gene rearrangements. Although the patient's cutaneous lesions were not biopsied at the time of initial presentation, chemotherapy did not significantly alter the clinical appearance of these lesions. Therefore, the composition of the infiltrate and the cytomorphology of the tumor cells in these lesions are favored to have remained essentially unchanged from time of presentation until biopsied approximately 1 year later (Table 1).

LL is primarily a nodal disease that presents with lymphadenopathy, commonly involving the cervical and axillary regions. 'B' symptoms of fever, weight loss and fatigue are common, along with splenomegaly. Mild anemia and leukopenia may be present, but often no significant laboratory abnormalities are noted. Lymph nodes show effacement of normal nodal architecture because of a diffuse proliferation of atypical small lymphoid cells with only slight nuclear irregularities. Numerous small, poorly defined clusters of epithelioid histiocytes are present. Vascularity is not pronounced and Reed-Sternberg-like cells, eosinophils and plasma cells in lymph node specimens have been reported as commonly being present.[3,6] T-cell-associated antigens are variably expressed, and aberrant loss of T-cell-associated antigens is often seen. T-cell gene rearrangements are common.[6] Patients typically present with advanced stage, with 74% of patients presenting at stage IV according to one large study.[3] Response to therapy is poor (25%) with frequent relapses (65%) and low 5-year survival.[13] Establishment of cutaneous involvement is

Table 1. Lennert lymphoma literature review

		Skin Involvement – no. of cases reported		Immunohistochemistry		T-cell rearrangement studies	
Author	Report year	At presentation	After therapy	Node	Skin	Node	Skin
Lennert and Mestdagh[1]	1968	3	NR	NP	NP	NP	NP
Kim et al.[3]	1978	2	1	NP	NP	NP	NP
Roundtree et al.[9]	1980	1	0	NP	NP	NP	NP
Kiesewetter et al.[8]	1989	1	0	NP	P	NP	NP
Massone et al.[7]	2005	0	1*	P	P	P†	P†
This study	2008	1	1‡	P	P	P	P

P, performed and diagnostic; NP, not performed; NA, not applicable; NR, not reported.
*Skin involvement was the first sign of recurrence in this case.
†Unable to compare skin and lymph node polymerase chain reaction products.
‡Persisted after therapy.

multimodal and involves a combination of routine light microscopy, immunohistochemistry and if available molecular analysis to arrive at a reliable diagnosis. Histologically, comparison of infiltrates of both lymph nodes and skin specimens show similarities, and concurrent or previous diagnosis of a lymph node is extremely helpful. Common descriptions include localized cellular infiltrates in the dermis. Often, the infiltrate tends to localize around blood vessels or skin appendages. Key to the diagnosis is the presence of epithelioid histiocytes and atypical small lymphoid cells. Vascularity is not increased, and the epidermis is usually unremarkable without cellular epidermotropism. Immunophenotyping shows a dense monoclonal T-cell population commonly associated with aberrant loss of associated antigens. T-cell receptor gene rearrangement studies can also be used to show clonality and are particularly helpful when correlated to gene rearrangement studies of the involved lymph nodes.[3,8,9]

The histological differential diagnosis includes Hodgkin lymphoma, angioimmunoblastic T-cell lymphoma (AILT), granulomatous mycosis fungoides, Rosai-Dorfman disease, xanthoma/xanthogranuloma, Langerhans cell histiocytosis and malakoplakia. AILT can be difficult to differentiate from LL because of the presence of epithelioid histiocytes, but high endothelial venules are abundant, readily identifiable and show arborization. Hodgkin lymphoma may also have a considerable number of epithelioid cells, usually distributed in an irregular and patch distribution, that can cause a diagnostic challenge. However, Hodgkin lymphoma will typically have readily identifiable Reed-Sternberg cells that will stain with CD30 and/or CD15. The diagnosis of granulomatous mycosis fungoides depends on the histological demonstration of granulomas with multinuclear foreign-body giant cells and the typical epidermotropic lymphocytes of mycosis fungoides.[14] Although in our case scattered lymphocytes were within the epidermis and vacuolar alteration was present at the dermoepidermal junction, the discrete nodularity and vertical growth of the lesions was too developed and unlike the typical patch or plaque growth patterns of mycosis fungoides. Cutaneous Rosai-Dorfman disease is characterized by scattered clusters or sheets of large polygonal histiocytes intermingled with a florid, mixed inflammatory infiltrate. There are often numerous admixed plasma cells. The most important feature to identify in this entity is emperipolesis. An S-100 protein stain can be used to highlight histiocytes in Rosai-Dorfman disease exhibiting emperipolesis.[15] In Langerhans cell histiocytosis, the dermis is involved by aggregates of large mononuclear histiocytes with reniform, irregular, cleaved nuclei and abundant eosinophilic cytoplasm (Langerhans cells). These Langerhans cells are admixed with other inflammatory cells, particularly eosinophils.[16] An S-100 stain is also useful to distinguish this entity because it will highlight the Langerhans cells. Alternatively, one can use immunostains for CD1a or Langerin. Malakoplakia consists of dermal sheets of large macrophages (von Hansemann cells) with a variable associated inflammatory infiltrate consisting mainly of lymphocytes, plasma cells and neutrophils. The macrophages have abundant foamy, eosinophilic cytoplasm with a prominent eccentric, hyperchromatic, round nucleus. Variable numbers of intracytoplasmic, concentrically laminated, round-ovoid, basophilic inclusions are usually easily appreciated and referred to as Michaelis-Gutmann bodies.[17] These inclusions can be highlighted with the use of von Kossa and/or periodic-acid-Schiff stains. Often, intracellular and extracellular bacterial organisms can be highlighted with a Gram stain. Other infectious processes should also be excluded from the differential with the assistance of special stains. Key histological features to note in order to distinguish LL from other T-cell lymphomas is the presence of epidermotropism, vascular proliferation or injury, uniformity or pleomorphism of the cellular infiltrate, presence of Reed-Sternberg-like cells and the location of the cellular infiltrate. A thorough immunohistochemical analysis, to include B-cell and T-cell-associated antigens, is imperative, and T-cell gene rearrangement studies are highly suggested.

Conclusion

The presence of epithelioid histiocytes and small lymphoid cells in the dermis is not pathognomonic for LL, and evaluation without a positive lymph node biopsy or suspicious history could prove to be extremely problematic. The patient's previous diagnosis of 'granulomatous dermatitis' preceding the diagnosis of lymphoma accentuates this point, and its diagnostic validity is quite intriguing. The association of cutaneous and nodal lymphomas with granulomatous reactions has been well described. In granulomatous lymphomas of the skin, 30.4% of cases in one series were misdiagnosed on the first biopsy. Thus, the need to consider close follow up and immunophenotypic and molecular genetic analysis of 'unusual' granulomatous dermatidides.[18]

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Note added after online publication: conflicts of interest

None declared.