The Korean Journal of Pathology 2011; 45: 101-105
DOI: 10.4132/KoreanJPathol.2011.45.1.101

Langerhans Cell Sarcoma Arising in a Lymph Node
– A Case Report and Review of the Literature –

Dong-Wook Kang · Hyun-Jin Son
Tae-Hwa Baek · Hye-Kyung Lee
Joo-Ryung Huh[1] · Joo-Heon Kim
Mee-Ja Park

Department of Pathology, Eulji University School of Medicine, Daejeon; [1]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Received: July 20, 2009
Accepted: November 16, 2009

Corresponding Author
Hyun-Jin Son, M.D.
Department of Pathology, Eulji University Hospital, 1306 Dunsan-dong, Seo-gu, Daejeon 302-799, Korea
Tel: +82-42-611-3451
Fax: +82-42-611-3459
E-mail: shjpathol@eulji.ac.kr

We report a case of Langerhans cell sarcoma presented as a solitary mass in the left supraclavicular area in a 31-year-old woman. Computed tomography revealed a relatively well-defined and lightly enhancing mass in the left supraclavicular area, measuring 5.5×4.5×3.2 cm. Excision was subsequently performed. Microscopically, the specimen consisted of an enlarged and partially effaced lymph node. Nests of different size composed of atypical tumor cells were located in the paracortex and the medulla of the lymph node. The tumor cells exhibited abundant eosinophilic or clear cytoplasm and displayed marked nuclear atypia and increased mitotic figures. Infiltration of many eosinophils was identified in the periphery and between the tumor cells. The tumor cells were reactive for CD1a and S100 protein. Ultrastructually, they were found to have Birbeck granules in the cytoplasm.

Key Words: Langerhans cell sarcoma; Lymph nodes; CD1a antigen

Tumors derived from Langerhans cells are classified into Langerhans cell histiocytosis (LCH) and Langerhans cell sarcoma (LCS), according to the degree of cytologic atypia and clinical aggressiveness.[1] Langerhans cells play a role in immune response and are involved in antigen processing and presentation to lymphocytes. Langerhans cells are mostly located suprabasally in the skin and mucosae as well as in the lymph nodes and thymus. They have small indented nucleus and clear cytoplasm that can be visualized well with immunohistochemical stains for S100 protein and CD1a. LCH can be localized to a single site, multiple sites within a single system or multiple systems.[1] The dominant sites of involvement in the solitary form are bone and adjacent soft tissue and, less commonly, lymph node, skin and lung.[1]

LCS is a rare, aggressive malignancy, and a few cases have been reported in the literature.[2-16] Most reported cases of LCS are extranodal, involving skin and bone and they tend to be multifocal.[1] LCS confined to a lymph node and presented as solitary mass is very rare. We herein report a case of LCS with this unusual presentation, describe the histopathologic findings and perform a literature review.

CASE REPORT

A 31-year-old woman presented with a one-week history of palpable mass in the left anterior neck. Her past medical history was unremarkable. Laboratory findings were unremarkable, except elevated levels of erythrocyte sedimentation rate and C-reactive protein. Qualitative analysis of anti-nuclear antigen, Epstein-Barr viral capsid and hepatitis viral antigens were negative. Neck computed tomography was performed, which revealed a well-demarcated lightly enhancing mass measuring 5.5 ×4.5×3.2 cm in the left supraclavicular area associated with multiple enlarged lymph nodes (Fig. 1). Infiltration to the neighboring tissues was not identified. Needle biopsy and subsequent excision were performed upon suspicion of malignant lymphadenopathy.

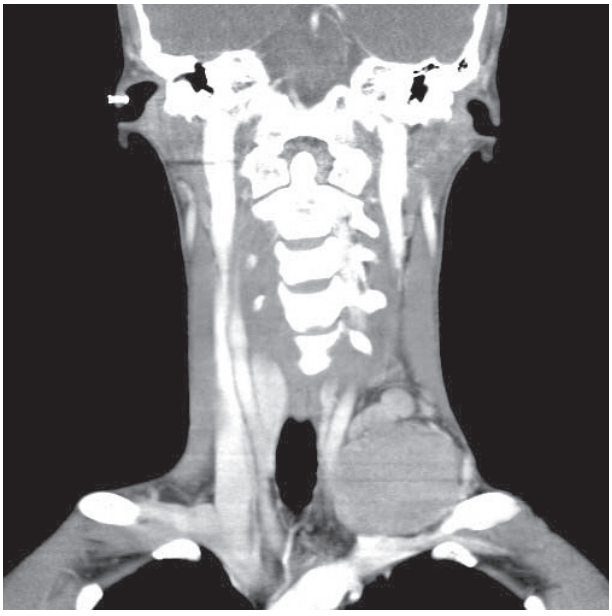

Fig. 1. Neck computed tomography demonstrates a well-demarcated and lightly enhancing mass, measuring 5.5×4.5×3.2 cm in the left supraclavicular area associated with multiple enlarged lymph nodes.

The excisional specimen consisted of a large ovoid mass, measuring 5.5×4.0×2.5 cm. On sectioning, the mass was soft and homogeneous with a yellow to grayish color tone. Microscopically, the tumor cells formed cellular aggregates of different sizes in islands or nodular fashion within the paracortex and medullary portion of the lymph node. The nuclei of the tumor cells displayed marked pleomorphism, one or two prominent nucleoli and a few longitudinal grooves (Fig. 2A). Numerous mitotic figures ranging from 15 to 20 per 10 high power field with atypical forms were identified. The tumor cells had abundant eosinophilic or clear cytoplasm. Infiltration of many eosinophils was identified in the periphery or between tumor cells (Fig. 2B). Multifocal hyalinization in the interfollicular area was also noted. Three lymph nodes adjacent to the mass were also excised which demonstrated unremarkable findings microscopically.

Immunohistochemically, the tumor cells were intensely reactive for CD1a (1:100, DakoCytomation, Glostrup, Denmark) (Fig. 2C) and S100 protein (1:200, Novocastra, Newcastle, UK) (Fig. 2D), and weakly reactive for CD68 (1:200, Novocastra). The followings were negative: pan-cytokeratin (CK) (1:50, Novocastra), CK7 (1:50, Novocastra), CK20 (1:50, Novocastra), CK5/6 (1:50, DakoCytomation), epithelial membrane antigen (EMA; 1:200, Novocastra), CD15 (1:100, Novocastra), CD30 (1:20, Novocastra), human melanoma black 45 (HMB45; 1:40, Signet Pathology System, Dedham, MA, USA), anaplastic lymphoma kinase (ALK; 1:40, NeoMarkers, Fremont, CA, USA), CD56 (1:50, Novocastra), and c-kit (1:50, CD117, DakoJapan, Kyoto, Japan). CD5 (1:40, Novocastra), granzyme B (1:25, DakoCytomation), and T cell intracellular antigen 1 (TIA-1; 1:40, Beckman Coulter, Marseille, France) were reactive for T lymphocytes but were negative on the tumor cells. CD20 (1:25, DiNonA, Seoul, Korea) and CD21 (1:25, DakoCytomation) were reactive for B-lymphocytes but negative on the tumor cells. The Ki-67 (1:100, Novocastra) proliferation index ranged from 5 to 10%. Small pieces of formalin-fixed and paraffin-embedded tissues were carefully selected and used for electron microscopic examination. Ultrastructurally, we found rod-like structures considered to be Birbeck granules in the cytoplasm of the tumor cells, despite of poor preservation of the other subcellular organelles (Fig. 3).

Neoadjuvant chemotherapy and radiation therapy after surgical excision were not considered. Neither other primary foci nor metastatic lesions were identified on whole body positron emission tomography/computed tomography taken a month after the excision.

DISCUSSION

LCS is neoplastic proliferation of Langerhans cells with overtly malignant cytologic features.[1] LCS involves the following sites: skin, lymph nodes, lung, liver, bone, mediastinum, bone marrow, spleen, and gallbladder. At initial diagnosis, LCS distinctively presents as multi-organ involvement. A few cases of solitary LCS are reported in the following sites: skin,[2,4,6,13,16] lymph nodes,[2,11] bone,[2,3] and lung.[9] Generally, solitary lesions caused by Langerhans cell proliferation show minimal cellular atypism and pursue benign clinical courses. Conversely, multisystemic disseminated lesions are characterized by aggressive clinical courses and destructive infiltration.[17] Marked cytologic atypia is generally associated with an aggressive clinical course and distant metastasis.[4-6] Pileri *et al.*[2] discussed that the survival difference between LCH and LCS, and suggested possible correlation between sarcomatoid morphology and poor outcome. However, Ben-Ezra *et al.*[17] in their analysis of 31 cases of histiocytosis X indicated that the morphologic appearance of Langerhans cells is an imperfect predictor of clinical outcome. In addition, there are examples of localized LCH showing aggressive clinical course, and multi-systemic LCH showing benign clinical course.[17,18] Newton and Hamoudi[19] discerned two morphologic subtypes of Langerhans cells: type I Langerhans cells are

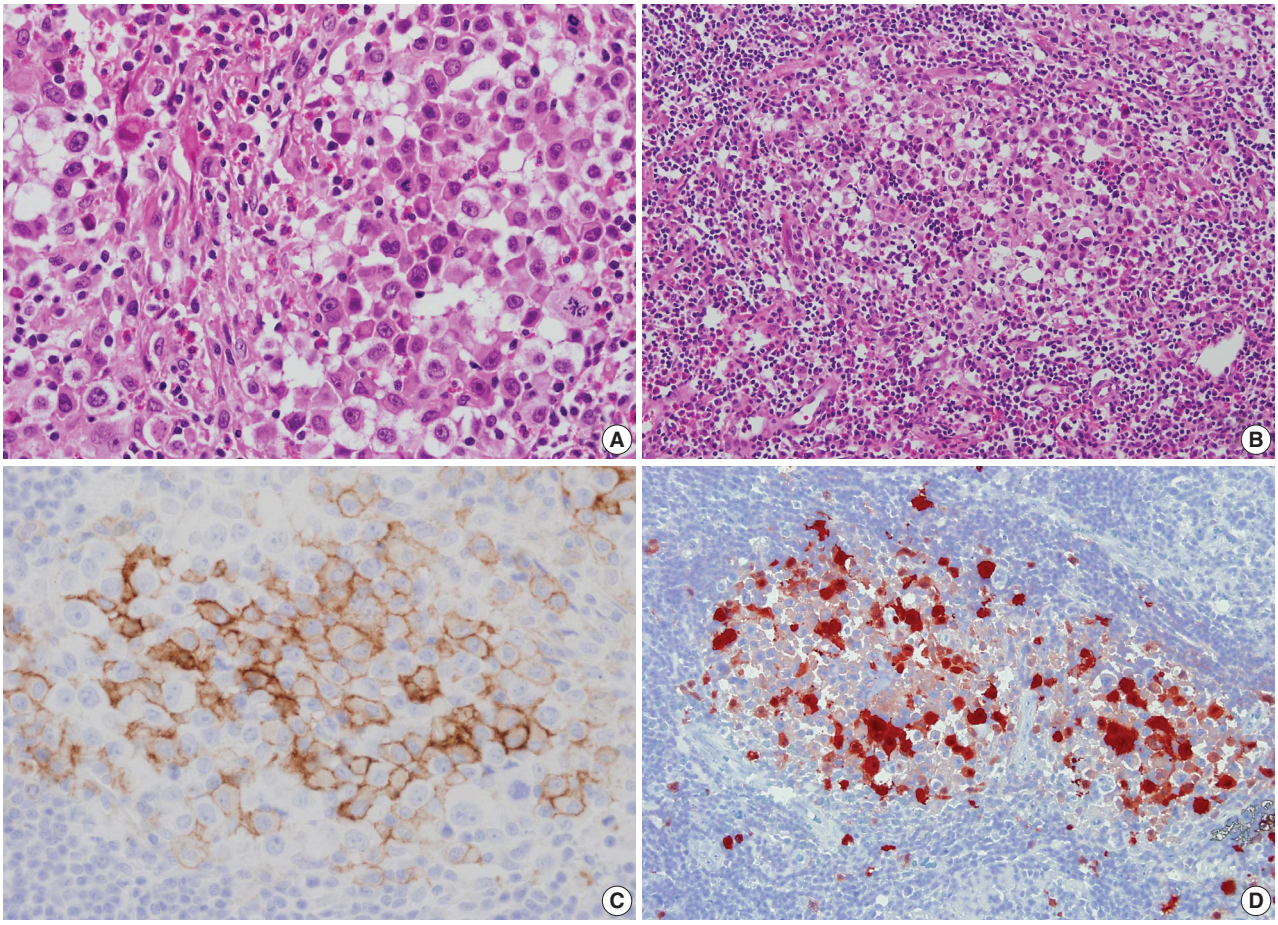

Fig. 2. (A) Nuclei of the tumor cells demonstrate marked pleomorphism, one or two prominent nucleoli, mitotic figures and a few longitudinal grooves. The tumor cells have eosinophilic or clear cytoplasm. (B) Infiltration of many eosinophils is identified in the periphery or between the tumor cells. Immunohistochemically, the tumor cells are reactive for CD1a (C) and S100 protein (D).

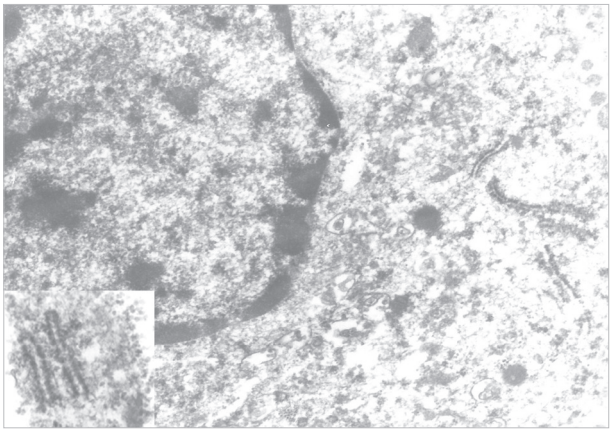

Fig. 3. Ultrastructurally, the tumor cells have characteristic Birbeck granules in the cytoplasm.

single and non-cohesive, and accompany a few eosinophils. Type II Langerhans cells are arranged in sheets and there are many eosinophils.[19] They found that type I patients had poor clinical course and type II patients had fairly benign course. Ben-Ezra *et al.*[17] stated that this general pattern was in accordance with the outcome of their experience, although there were exceptions. The case presented herein was solitary LCS and confined to a lymph node in the left supraclavicular area, and displayed marked cytologic atypia of Langerhans cells and some eosinophilic infiltrate. Judging from the information presented above, we assumed that our patient would have favorable clinical outcome following complete excision but needs careful follow-up studies.

To the best of our knowledge, about 30 cases of LCS have been reported in the English-language literature to date (Table 1).[2-16] Patient age ranged between 10 and 88 years, with a male-female ratio of 1.36 : 1. Despite intensive therapy, most patients experienced multi-organ involvement, which is a feature of poor prognosis, and short survival time. A 57-year-old man with leukemic transformation of LCS was reported in the literature and he died of disease progression 7 months after the initial diagnosis.[12] In contrast, LCS presented as solitary lesion in skin, bone,

Table 1. Summary of the reported cases of Langerhans cell sarcoma

Case No.	Reference	Age (yr)	Sex	Involving site	Treatment	Outcome
1	Pileri *et al.*[2]	17	F	Lymph node	Chemotherapy, radiation	Relapse after CR
2	Pileri *et al.*[2]	46	M	Lymph node	Chemotherapy	Alive with disease
3	Pileri *et al.*[2]	28	M	Mediastinum, hepatosplenomegaly	None	DOD
4	Pileri *et al.*[2]	50	F	Skin	NA	NA
5	Pileri *et al.*[2]	10	F	Skin	Surgery, radiation	CR
6	Pileri *et al.*[2]	23	F	Lymph node, skin, lung	Chemotherapy	DOD
7	Pileri *et al.*[2]	65	F	Lymph node, lung, hepatosplenomegaly	Chemotherapy	DOD
8	Pileri *et al.*[2]	72	M	Lymph node, lung, rib, central nervous system	Chemotherapy	DOD
9	Pileri *et al.*[2]	50	F	Bone	Surgery	CR
10	Kawase *et al.*[3]	59	M	Skin, lymph node, bone marrow, splenomegaly	Chemotherapy	DOD
11	Kawase *et al.*[3]	35	M	Bone, lymph node, pleura	Chemotherapy	DOD
12	Kawase *et al.*[3]	62	F	Lymph node, hepatosplenomegaly	Chemotherapy	DOD
13	Kawase *et al.*[3]	60	M	Bone	Radiation	Alive with disease
14	Itoh *et al.*[4]	74	F	Skin	Surgery, radiation	DOD
15	Tani *et al.*[5]	49	F	Skin, lymph node, lung	Chemotherapy	DOD
16	Misery *et al.*[6]	38	F	Skin	Surgery	CR
17	Ferringer *et al.*[7]	33	M	Skin, lymph node	Chemotherapy	CR
18	Jülg *et al.*[8]	81	M	Mediastinum, lung	Chemotherapy	DOD
19	Lee *et al.*[9]	34	M	Lung	Surgery	CR
20	Bohn *et al.*[10]	47	M	Skin, lymph node	Surgery, chemotherapy	DOD
21	López-Ferrer *et al.*[11]	67	M	Lymph node	NA	NA
22	Sumida *et al.*[12]	57	M	Lymph node, tonsil, splenomegaly, bone marrow	Chemotherapy	DOD
23	Deng *et al.*[13]	88	M	Skin	Surgery	CR
24	Diaz-Sarrio *et al.*[14]	58	M	Skin, lymph node	Surgery	CR
25	Zhao *et al.*[15]	74	F	Gallbladder, lymph node	Surgery	CR
26	Uchida *et al.*[16]	72	M	Skin	Chemotherapy, surgery	CR
Present case		31	F	Lymph node	Surgery	On follow-up

F, female; M, male; CR, complete remission; DOD, died of disease; NA, not available.

lung and lymph nodes have favorable clinical course irrespective of therapy.[2-4,6,9,11,13,16] Misery *et al.*[6] contends that LCS is not always a lethal disease.

Unlike LCH, the characteristic nuclear features of Langerhans cells are inexplicitly identified in LCS. In addition, due to marked cytologic atypia and paucity of eosinophils, we considered many differential diagnoses: malignant melanoma, anaplastic large cell lymphoma, Hodgkin lymphoma, metastatic carcinoma including anaplastic carcinoma, germ cell tumors, and histiocytic and other dendritic cell neoplasms. López-Ferrer *et al.*[11] reported the outcome of fine needle aspiration cytology of a patient with LCS. They concluded that although some nuclear indentations were present, they were insufficient to raise the suspicion of LCS bsed on the cytomorphologic features.[11] As such, immunohistochemical antibodies, including epithelial, mesenchymal, lymphoid, histiocytic, and dendritic cell markers, are necessary to enable the establishment of differential diagnosis. Malignant melanoma expresses HMB45 and other melanocytic markers. Anaplastic large cell lymphoma is reactive for antibodies on CD30 and EMA and may show ALK positivity. Hodgkin lymphoma shows CD15 and CD30 positivity. Epithelial markers, including CK and EMA, are necessary to exclude primary and metastatic carcinoma. Establishment of the differential diagnoses of histiocytic sarcoma and other dendritic cell neoplasms is possible with the following antibodies: CD1a, S100 protein, CD21, CD35, CD68, and lysozyme. In the case presented herein, the tumor cells were reactive for CD1a and S100 protein antibodies, and focally reactive for CD68 antibodies. The remaining antibodies were negative: epithelial markers (pan-CK, CK5/6, CK7, CK20, and EMA), melanocytic marker (HMB45), lymphoid cell markers (CD5, CD20, CD15, CD30, CD56, ALK, granzyme B, and TIA-1), follicular dendritic cell marker (CD21), and c-kit.

In conclusion, we report an unusual presentation of LCS in a supraclavicular lymph node. Specific markers for Langerhans cells, CD1a or Langerin (CD207) is necessary to make confirmative diagnosis and other neoplasia, including melanoma, lymphoma and carcinoma, germ cell tumors, histiocytic and other dendritic cell neoplasms should be excluded. The biologic behavior of LCS is known to be aggressive. However, the prognoses of a few cases of LCS with good resectibility remain unclear and need to be further investigated.

REFERENCES

1. Jaffe R, Weiss LM, Facchetti F. Tumours derived from Langerhans cells. In: Swerdlow SH, Campo E, Harris NL, *et al*., eds. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press, 2008; 358-60.
2. Pileri SA, Grogan TM, Harris NL, *et al.* Tumours of histiocytes and accessory dendritic cells: an immunohistochemical approach to classification from the International Lymphoma Study Group based on 61 cases. Histopathology 2002; 41: 1-29.
3. Kawase T, Hamazaki M, Ogura M, *et al.* CD56/NCAM-positive Langerhans cell sarcoma: a clinicopathologic study of 4 cases. Int J Hematol 2005; 81: 323-9.
4. Itoh H, Miyaguni H, Kataoka H, *et al.* Primary cutaneous Langerhans cell histiocytosis showing malignant phenotype in an elderly woman: report of a fatal case. J Cutan Pathol 2001; 28: 371-8.
5. Tani M, Ishii N, Kumagai M, Ban M, Sasase A, Mishima Y. Malignant Langerhans cell tumour. Br J Dermatol 1992; 126: 398-403.
6. Misery L, Godard W, Hamzeh H, *et al.* Malignant Langerhans cell tumor: a case with a favorable outcome associated with the absence of blood dendritic cell proliferation. J Am Acad Dermatol 2003; 49: 527-9.
7. Ferringer T, Banks PM, Metcalf JS. Langerhans cell sarcoma. Am J Dermatopathol 2006; 28: 36-9.
8. Jülg BD, Weidner S, Mayr D. Pulmonary manifestation of a Langerhans cell sarcoma: case report and review of the literature. Virchows Arch 2006; 448: 369-74.
9. Lee JS, Ko GH, Kim HC, Jang IS, Jeon KN, Lee JH. Langerhans cell sarcoma arising from Langerhans cell histiocytosis: a case report. J Korean Med Sci 2006; 21: 577-80.
10. Bohn OL, Ruiz-Argüelles G, Navarro L, Saldivar J, Sanchez-Sosa S. Cutaneous Langerhans cell sarcoma: a case report and review of the literature. Int J Hematol 2007; 85: 116-20.
11. López-Ferrer P, Jiménez-Heffernan JA, Alves-Ferreira J, Vicandi B, Viguer JM. Fine needle aspiration cytology of Langerhans cell sarcoma. Cytopathology 2008; 19: 59-61.
12. Sumida K, Yoshidomi Y, Koga H, *et al.* Leukemic transformation of Langerhans cell sarcoma. Int J Hematol 2008; 87: 527-31.
13. Deng A, Lee W, Pfau R, *et al.* Primary cutaneous Langerhans cell sarcoma without Birbeck granules: indeterminate cell sarcoma? J Cutan Pathol 2008; 35: 849-54.
14. Diaz-Sarrio C, Salvatella-Danés N, Castro-Forns M, Nadal A. Langerhans cell sarcoma in a patient who underwent transplantation. J Eur Acad Dermatol Venereol 2007; 21: 973-6.
15. Zhao G, Luo M, Wu ZY, *et al.* Langerhans cell sarcoma involving gallbladder and peritoneal lymph nodes: a case report. Int J Surg Pathol 2009; 17: 347-53.
16. Uchida K, Kobayashi S, Inukai T, *et al.* Langerhans cell sarcoma emanating from the upper arm skin: successful treatment by MAID regimen. J Orthop Sci 2008; 13: 89-93.
17. Ben-Ezra J, Bailey A, Azumi N, *et al.* Malignant histiocytosis X: a distinct clinicopathologic entity. Cancer 1991; 68: 1050-60.
18. Howarth DM, Gilchrist GS, Mullan BP, Wiseman GA, Edmonson JH, Schomberg PJ. Langerhans cell histiocytosis: diagnosis, natural history, management, and outcome. Cancer 1999; 85: 2278-90.
19. Newton WA Jr, Hamoudi AB. Histiocytosis: a histologic classification with clinical correlation. Perspect Pediatr Pathol 1973; 1: 251-83.