Langerhans cell sarcoma originating from left knee subcutaneous tissue: A case report and literature review

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Abstract. Langerhans cell sarcoma (LCS) is a neoplastic proliferation of Langerhans cells with notably malignant cytological features. Reports of LCS are sparsely available in English literature; to the best of our knowledge, only 55 cases have been reported. The present study reports a case of LCS originating from subcutaneous tissue of the left knee in a 75-year-old man. The diagnosis of LCS was supported by the results of magnetic resonance imaging, histological and immunohistochemical studies. The tumor began to metastasize to inguinal lymph nodes and eventually involved multiple organs. Chemotherapy and radiotherapy were administered but were ineffective, and the patient died within 2 years of diagnosis. The present case should aid in expanding the currently available knowledge concerning LCS.

Introduction

The World Health Organization classifies Langerhans cell tumors into two types: Langerhans cell sarcoma (LCS) and Langerhans cell histiocytosis (LCH) (1). LCS is a neoplastic proliferation of Langerhans cells with markedly malignant cytological features, whereas LCH is proliferative disorder of Langerhans cells (1). LCS may occur in individuals of a broad age range, and is highly metastatic (2). The disease may involve multiple organs or tissues (3), including bone, lung, skin, lymph nodes, gallbladder, tonsil and other soft tissues. In the clinic, LCS is an extremely rare disease that is unfamiliar to dermatologists (2). The clinical behavior of the disease is aggressive and the overall survival rate for affected patient’s is <50% (3). Several therapeutic regimens have been investigated for the treatment of LCS, including surgery, chemotherapy, radiation therapy and combined therapy (3). However, due to the limited number of cases reported in the literature to date, no standard effective therapy has been suggested for the treatment of LCS (3). Among LCS patients, the therapeutic outcomes vary depending on the extent of the disease. In addition, the prognosis of the disease is poor and relapses usually occur within the first 3 years after excision (3).

The current study reports one case of LCS that originated from the subcutaneous tissue of the left knee of a male patient. In addition, all reported cases of LCS available in the English literature are summarized.

Case report

A 75-year-old male patient was admitted to Beijing Hospital (Beijing, China) on November 4, 2010, complaining of an egg-sized mass located at the medial part of his left knee. The patient reported that the mass had gradually enlarged during the past two months and caused mild-to-moderate pain at night. The pain would somehow be relieved during the daytime and after taking non-steroidal anti-inflammatory drugs. The patient had a medical history that included tonsillectomy 55 years previously, subtotal thyroidectomy 40 years previously (pathology indicated a thyroid adenoma), partial prostatectomy 15 years previously (benign pathology), radical operation for colorectal cancer 5 years previously (pathology indicated intramucosal carcinoma) and a resection of mass of the buttock 4 years previously (pathology indicated an abscess).

Physical examination revealed a firm mass of ~3x3 cm on the patient’s left knee. Inguinal lymph nodes were palpated on both sides and were found to be small, round and soft. X-ray imaging indicated hyperosteogeny in the knee joint and an ultrasound of the mass revealed a low-echo region in the subcutaneous tissue. Magnetic resonance imaging (MRI) revealed a mass measuring ~40x12x15 mm with a clear boundary in the subcutaneous tissue on the anterior-medial side of the patient’s left patella (Fig. 1). The mass exhibited homogeneous signal isointensity relative to that of muscle on T1-weighted imaging (Fig. 1A), and predominantly signal hyperintensity on T2-weighted imaging (Fig. 1B). A number of small patchy hyperintense signals were observed within the mass (Fig. 1B).

The patient received a knee arthroscopic surgery on November 10, 2010. Grossly, a 4x3x2-cm, gray mass was identified, located subcutaneously and with a clear border. No infiltration into the joint space was observed. Thus, the patient underwent a surgical resection of the mass. A...
4.8x3.6x1.2-cm specimen was obtained. The cut surface of the resected specimen was gray, soft, and had a pseudo-membrane. Histological examination of the specimen by hematoxylin and eosin staining indicated an infiltrative tumor mass. The tumor cells were surrounded by abundant lymphocytes, plasma cells and eosinophils (Fig. 2). The neoplastic cells exhibited cytological atypia, hyperchromatic nuclei and prominent nucleoli. Nuclear grooving was also observed in some of the neoplastic cells (Fig. 2). Immunohistochemical stains were positive for cluster of differentiation (CD)1a (+; rabbit monoclonal antibody; catalog no. AC-0078; 1:200 dilution; Baili Biotechnology Co., Ltd., Changhun, China; Fig. 3A), CD68 (+; mouse monoclonal antibody; catalog no. Z-2071; 1:200 dilution; Zeta Corporation, Los Angeles, CA, USA; Fig. 3B), S-100 (++; rabbit polyclonal antibody; catalog no. NCL-L-S100p; 1:150 dilution; Leica Microsystems, Ltd., Milton Keynes, UK; Fig. 3C) and vimentin (+++; mouse monoclonal antibody; catalog no. 202M-96; 1:150 dilution; Cell Marque, Sigma-Aldrich, St. Louis, MO, USA). The tests were negative for desmin (mouse monoclonal antibody; catalog no. 243M-16; 1:100 dilution; Cell Marque, Sigma-Aldrich), CD30 (mouse monoclonal antibody; catalog no. CM073C; 1:200 dilution; Biocare Medical LLC, Concord, CA, USA), actin (mouse monoclonal antibody; catalog no. 202M-96; 1:150 dilution; Cell Marque, Sigma-Aldrich), HMB-45 (mouse monoclonal antibody; catalog no. Z-2088; 1:150 dilution; Zeta Co., Ltd.), melan-A (mouse monoclonal antibody; catalog no. Z-2052; 1:200 dilution; Zeta Co., Ltd.) and myoglobin (mouse monoclonal antibody; catalog no. UM800033; 1:200 dilution; Origene Technologies Inc.) was ~70% (Fig. 3D). Taken together, the histomorphological, immunohistochemical and MRI findings supported a diagnosis of LCS.

Following the surgery, local radiotherapy was proposed for the patient. Unfortunately, this planned therapy was abolished as the patient was suffering from septic arthritis and fever. However, a careful plan to follow up this patient was established. At ~6 months after the first surgery, a positron emission tomography-computed tomography (PET-CT) study of the patient revealed a tumor mass in the left inguinal lymph nodes. Surgical resection of the left inguinal lymph nodes was performed in another hospital, Peking Union Medical College Hospital (Beijing, China), due to practical reasons. LCS metastasis to the inguinal lymph nodes was confirmed by the subsequent pathological findings. Unexpectedly, the patient had developed septic arthritis and fever again. Following postoperative recovery, the patient received four cycles (21 days for one cycle) of chemotherapy with cyclophosphamide (1.4 g on day 1), epirubicin hydrochloride (120 mg on day 1), vindesine (4 mg on day 1) and prednisone (100 mg/day on days 1-5) at Peking Union Medical College Hospital.

In January 2012, a follow-up PET-CT scan was performed. A 4.2x3.3 cm soft tissue mass was detected beside the external iliac with a maximal standardized uptake value (SUV_{max}) of around 12.6. Several small lymph nodes located close to the mass had an SUV_{max} of ~11.5. Furthermore, the inguinal lymph nodes in the left groin also had high SUVs of 5.1-7.1. Between February and March 2012, the patient received left groin and lateral pelvis local radiotherapy (total dose, 6,000 cGy; 30 fractions over 47 days) at Peking Union Medical College Hospital. However, the treatment was ineffective, and the LCS was found to have metastasized into multiple organs and tissues (liver, omentum and ascites) 2 months later. The patient succumbed to the disease in November 2012.

Discussion

LCS is a rare neoplastic proliferation of Langerhans cells with notable malignant cytological features (3). Sparse reports of
| Case | Author, year | Gender/age, years | Site | Clinical history | Diagnostic techniques | Therapy | Outcome | Ref. |
|------|-------------|------------------|------|------------------|-----------------------|---------|---------|------|
| 1    | Wood, 1984  | M/71             | Cutaneous, lung | NA | EM, X-ray | C | Died at 2 months | (4) |
| 2    | Elleder, 1986 | F/NA             | Cutaneous and mucosal tumors | NA | EM | NA | NA | (5) |
| 3    | Delabie, 1991 | F/23             | Inguinal, iliac and retroperitoneal adenopathies, skin lesions and interstitial lung involvement | NA | EM, cytogenetic study | C | Died of disease | (6) |
| 4    | Tani, 1992  | F/49             | Skin, inguinal adenopathy | NA | EM, lab | C | Died at 4 years | (7) |
| 5    | Lauritzen, 1994 | M/38             | Skin, lymph nodes, lung | NA | NA | C | Partial remission after 12 months | (8) |
| 6    | Itoh, 2001  | F/74             | Skin, axillary adenopathy | Right hand erythema lasting a few years | CT, EM | S, R, C | Died at 14 months | (9) |
| 7    | Pileri, 2002 | F/17             | Cervical, groin, iliac and retroperitoneal adenopathies, and systemic symptoms | NA | EM | C, R | ACR | (10) |
| 8    |             | M/46             | Submandibular and left cervical adenopathies | NA | EM | C | AWD | |
| 9    |             | M/28             | Fever, cytopenia, anterior mediastinal mass and hepatosplenomegaly | NA | EM | None | Died at 3 weeks | |
| 10   |             | F/50             | Skin | NA | EM | NA | NA | |
| 11   |             | F/10             | Skin | NA | EM | S, R | ACR | |
| 12   |             | F/23             | Skin, lymph nodes, lung | NA | EM | C | Died at 2 years | |
| 13   |             | F/65             | Generalized adenopathies, lung lesions and hepatosplenomegaly | NA | EM | C | Died of disease | |
| 14   |             | M/72             | Fever, mediastinal and axillary adenopathies, lung nodules, rib fractures and central nervous system lesions | NA | EM | C | Died of disease | |
| 15   |             | F/50             | Polyostotic bone lesions | NA | EM | S | ACR | (11) |
| 16   | Misery, 2005 | F/38             | Skin | NA | Lab | S | ACR | |
| 17   | Kawase, 2005 | M/59             | Spleen, skin, lymph nodes, bone marrow | Essentially normal, splenomegaly, no hepatomegaly | None | C | Died at 9 years | |
| 18   | Kawase, 2005 | M/35             | Bone, lymph nodes, lung, liver | NA | X-ray, MRI, CT | C | Died at 4 years | |
| 19   | Kawase, 2005 | F/62             | Spleen, lymph nodes, liver | 2-year multiple bone pain | X-ray, CT | C | Died at 10 months | |
| 20   | Kawase, 2005 | M/60             | Bone | NA | X-ray, MRI | R | ACR | |
| 21   | Julg, 2006  | M/81             | Mediastinal mass and interstitial lung involvement | NA | CT, EM | C | Died at 1 month | |
| 22   | Ferringer, 2006 | M/33            | Posterior thigh skin, lymph nodes | NA | EM | C | ACR | (14) |
| Case | Author, year | Gender/age, years | Site | Clinical history | Diagnostic techniques | Therapy | Outcome | Ref. |
|------|--------------|-------------------|------|-----------------|-----------------------|---------|---------|------|
| 23   | Lee, 2014    | M/34              | Lung | Smoker, treated and cured pulmonary tuberculosis | CT | S       | ACR   | (15) |
| 24   | Diaz-Sarrio, 2007 | M/58            | Skin, lymph nodes | Liver transplantation and immunosuppressive therapy | X-ray, EM | S       | ACR   | (16) |
| 25   | Bohn, 2007   | M/47              | Skin, lymph nodes | NA | CT, EM | S, R, C | AWD   | (17) |
| 26   | López-Ferrer, 2008 | M/67            | Cervical lymph node | NA | NA | S       | NA    | (18) |
| 27   | Sumida, 2008 | M/57              | Supraclavicular lymph node | NA | Lab, EM, IGH | C       | Died at 7 months | (19) |
| 28   | Yoshimi, 2008 | F/53              | Skin, lymph nodes, lung, stomach, liver, spleen, kidneys, bone marrow | Liver failure due to primary biliary cirrhosis | CT, Lab, FDG-PET | C       | Died at 5 months | (20) |
| 29   | Zhao, 2009   | M/72              | Skin | Otherwise healthy | FDG-PET, MRI | C       | ACR   | (21) |
| 30   | Langfort, 2009 | M/47             | Lung, lymph nodes | Smoker, 30 packs/year | CT, EM | S, C    | AWD   | (23) |
| 31   | Diaz-Sarrio, 2007 | M/63            | Skin, lymph nodes | Liver transplantation and immunosuppressive therapy | PET | C, R    | Died at 5 years | (16) |
| 32   | Nakayama, 2010 | M/62             | Cervical lymph node | 3-month neck swelling | CT, FDG-PET | R       | ACR   | (24) |
| 33   | Ratei, 2010  | M/20              | Supraclavicular lymph node | ACR from B-cell acute lymphoblastic leukemia | IGH, CT | C, allo-PBSCT | ACR   | (25) |
| 34   | Chen, 2012   | M/53              | Lung, lymphadenopathy | Heavy smoker, severe cough | PET-CT | NA      | NA    | (26) |
| 35   | Muslimani, 2012 | F/66            | Left pyriform sinus | Hairy cell leukemia | PET-CT, cytogenetic study, IGH | C       | Died of disease | (27) |
| 36   | Furmanczyk, 2012 | M/75            | Skin, bone marrow | 1-year leukemia | MRI, IGH | S, R, C | Died of disease | (28) |
| 37   | Shimizu, 2012 | F/67              | Inguinal lymph node, cervical node | NA | CT, PET | C       | ACR   | (29) |
| 38   | Wang, 2012   | M/41              | Multifocal cutaneous, anterior iliac spine, liver, lung | NA | NA | S, C    | Died at 1 year | (30) |
| 39   | Xu, 2012     | M/86              | Lymphadenopathy and splenomegaly | Diabetes, 25-year arteritis and myocardial infarction | Lab, CT | S, R    | Died at 1 month | (31) |
| 40   | Yang, 2013   | M/52              | Lung, lymph nodes, rib | Healthy smoker | Lab, PET-CT | C       | AWD   | (32) |
| 41   | Wang, 2013   | F/77              | Lymph nodes and nasopharyngeal recess mass | 1-month neck swelling and pain | EM, CT | None    | Died at 2 weeks | (2) |
| 42   | Chang, 2013  | F/70              | Lymph node | Chronic myelogenous leukemia undergoing imatinib mesylate therapy | Lab, cytogenetic study | S, C    | ACR   | (33) |
| 43   | Chen, 2013   | F/68              | Inguinal lymph node | Chronic lymphocytic leukemia | Cytogenetic study | C       | AWD   | (34) |
| Case | Author, year | Gender/age, years | Site | Clinical history | Diagnostic techniques | Therapy | Outcome | Ref. |
|------|-------------|------------------|------|------------------|----------------------|---------|---------|------|
| 45   | Chung, 2013 | F/11 mo.          | Fever, lymph nodes | NA | Lab, CT, MRI | C | AWD (35) |
| 46   | F/17        | Fever, hepatosplenomegaly, petechiae, lymph nodes, liver, skin | Unremarkable past medical and family histories | Lab, CT, MRI | C | AWD |
| 47   | Keklik, 2013 | M/39 Nasopharynx | NA | NA | Lab | C | Died (36) |
| 48   | Li, 2013   | M/48 Ulcerated erythematous plaque on right knee, skin nodule | Acute myeloid leukemia | Lab | C | ACR (37) |
| 49   | Sagransky, 2013 | M/54 Subcutaneous nodules, neutropenic fever, *Clostridium difficile* colitis | Unclassifiable myelodysplastic/myeloproliferative neoplasm, 1-week eruptive papular violaceous rash | NA | C | Died at 3 months (38) |
| 50   | M/61        | Scalp ulceration nodular | Unremarkable past medical history | NA | S | ACR |
| 51   | M/88        | Scalp skin nodule | NA | EM | S | Died at 3 months |
| 52   | Valentin-Nogueras, 2013 | M/71 Skin, lymph nodes | Hypertension, myelodysplastic syndrome | Lab, X-ray, CT | S, R, C | Died at 7 months (3) |
| 53   | West, 2013 | M/52 Lymphadenopathy | NA | Lab, CT, PET | C, R | Died at 8 years (39) |
| 54   | Lee, 2014  | M/45 Lymph nodes, lung | Asymptomatic erythematous plaques for 4 years on scalp and 1 year on axillae | MRI, PET-CT | C, R | Died at 2 years |
| 55   | Present case | M/75 Subcutaneous tissue, inguinal lymph nodes, multiple organs | Tonsillectomy, subtotal thyroidectomy, partial prostatectomy, ACR from colorectal cancer, resection of abscess mass of buttock | MRI, PET-CT | C, R | Died at 2 years |

M, male; F, female; mo., months; NA, not available; EM, electron microscopy; Lab, laboratory investigations; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; C, chemotherapy; S, surgical excision; R, radiation therapy; allo-PBSCT, allogeneic peripheral blood stem cell transplantation; ACR, alive in complete remission; AWD, alive with disease; IGH, immunoglobulin H.
LCS are available in English literature; to the best of our knowledge, only 55 cases have been reported to date. The available reports are summarized, together with the present case, in Table I [(2) and references therein; (3-39)]. A search of Pubmed was performed to find these reports using the keyword ‘Langerhans cell sarcoma’ and manual screening was applied. In these cases, the age at diagnosis of LCS ranged from 11 months to 88 years, with a median age of 53 years, and a male:female ratio of 1.4:1. The collective findings also indicate that LCS is extremely aggressive and that it typically metastasizes to multiple organs or tissues.

The differential diagnosis of LCS from LCH may often be challenging due to their histological and immunohistochemical similarities (40). Cytologically, however, LCS exhibits a markedly higher degree of cytological atypia and more frequent mitotic features compared with LCH (10). In the majority of cases, LCS and LCH are immunohistochemically positive for CD1a, S-100 protein and langerin (CD207), while negative for CD21 and CD35; however, LCS commonly has a higher Ki-67 index than LCH (41). Supplementary use of other diagnostic techniques demonstrates great advantages for differentiating between LCS and LCH (35). As shown in Table I, laboratory investigations, electron microscopy, ultrasound, X-ray, CT, MRI, FDG-PET and cytogenetic analysis have been used as accessory techniques in the diagnosis of LCS. In the current case, MRI was utilized during diagnosis and PET-CT was used in follow-up examinations.

Notably, the patient in the present case had an abnormal clinical history compared with other reported cases. The patient had experienced thyroid adenoma, benign prostate

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Figure 2. Hematoxylin and eosin staining of the specimen. Original magnifications, (A) x200 and (B) x400.

Figure 3. Immunohistochemical studies. Cells were immunopositive for (A) CD1a, (B) CD68 and (C) S-100. (D) The Ki-67 index was ~70%. All images were captured at high magnification (x400). CD, cluster of differentiation.
mass and intramuscular carcinoma. Studies of immunoglobulin heavy chain rearrangement have demonstrated that LCS may not only develop de novo, but may originate from LCH (42) or leukemia (27). Hence, it may be of great importance to analyze the clonal relationship between LCS and other types of tumor cells, such as thyroid adenoma and intramuscular carcinoma as seen in the present case. Unfortunately, such studies were not conducted with the specimen from this patient.

Another phenomenon noted in the present case was that, following the two surgical resections, the patient suffered from septic arthritis and fever. The patient had undergone a resection of a mass of the buttock 4 years prior to his presentation with the left knee mass, and the pathology had indicated an abscess. Whether the septic arthritis was a result of the LCS or was due to the patient’s idiosyncrasies was not clear. Nevertheless, close attention must be paid to a patient’s clinical history in clinical practice, as such information may aid in the evaluation of the patient’s immune surveillance system. The occurrence of LCS has been reported previously in a patient having ongoing immunosuppression therapy following a liver transplant (16).

Due to the rarity of LCS, no standard treatment with good efficacy has been suggested to date (3). Local resection is commonly applied to isolated LCS lesions (Table I). Chemotherapies, such as a modified ESHAP (etoposide, carboplatin, cytarabine, and methylprednisolone) (20) and MAID (mesna, doxorubicin, ifosfamide, dacarbazine) (21) regimens, have been demonstrated to be effective in a proportion of patients. Radiotherapy has also been reported to be effective in certain cases. Complete remission, without signs of recurrence or metastasis for 45 months without adjuvant therapy, was achieved by a total dose of 59.4 Gy radiotherapy to a cervical lymph node LCS patient (25). In the current case, metastasis to inguinal lymph nodes was detected at ~6 months after the first surgical resection. Furthermore, multiple organs metastasis was detected following four cycles of chemotherapy with adjuvant radiotherapy. Considering the poor outcome and prognosis of LCS, more aggressive and effective standard therapies are urgently required, and a careful follow-up plan is necessary.

In summary, the present study reported a rare case of LCS originating from the subcutaneous tissue of the left knee. The diagnosis, treatment and disease progress of the case were described, which should aid in expanding the currently available knowledge concerning LCS.

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