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Langerhans cell sarcoma of the vulva: Case report and review of the literature

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ABSTRACT

Langerhans cell sarcoma (LCS) is a rare, malignant neoplastic disorder of Langerhans cells thought to arise from antecedent Langerhans cell histiocytosis (LCH) or *de novo*. There are less than 70 cases of LCS reported in the medical literature, with this case being the first report of primary vulvar LCS. We present the case of a 73-year-old female with a painful 2 cm ulcerated lesion of the right labia majora. The patient was treated with oral antibiotics without resolution. On referral to gynecologic oncology an office biopsy showed LCS. Surgical excision was performed with clear margins and diagnostic confirmation of LCS by histopathological features and immunohistochemical evaluation. The patient received adjuvant radiation therapy (45.6 Gy). After 33 months of surveillance, the patient remains with no evidence of disease. Due to the rarity of this disease, there is a lack of standardized recommendations for adjuvant therapy, including radiotherapy and chemotherapy regimens for both localized and systemic LCS. This case report supports the management of localized disease by surgical excision followed by radiotherapy as effective for preventing recurrence and metastatic progression. Early recognition and treatment are critical for cure, and can be accomplished by prompt referral to a specialist as well as low threshold for biopsy. Further investigation is needed for establishing a standardized management guideline for LCS.

1. Case

A 73-year-old P3003 female presented with a 2 month history of a right vulvar lesion and pain along the labia majora. The patient received a 2 week course of oral antibiotics without resolution of her symptoms. On pertinent review of systems, the patient also reported fatigue. Physical examination revealed a 2 cm ulcerated lesion on the right labia majora (Fig. 1). The lesion was tender to palpation. Speculum exam showed an atrophic vagina without lesions. There were no palpable masses in the pelvis or groin.

Past medical history was significant for hypertension and gastroesophageal reflux disease. Patient underwent hysterectomy due to cervical dysplasia at the age of 30. Patient was up to date with screening for breast and colon cancer. Social history was significant for 15 pack-years smoking history. Family history included bladder and liver cancer in her mother and head and neck, prostate, and bone cancer in her father.

2. Diagnostic work up

Biopsy showed Langerhans cell sarcoma. CT scan of the chest, abdomen, and pelvis were negative for any local or distant metastasis.

3. Intervention

Patient underwent right partial radical vulvectomy, with wide margin resection.

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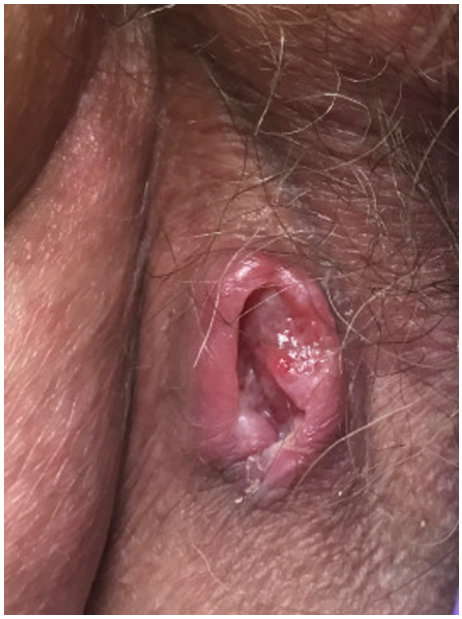

Fig. 1. Right vulvar lesion.

4. Pathology

The partial vulvectomy specimen showed a 2.2 × 1.5 cm tan pink nodular firm mass involving the subcutaneous tissue. The lesion showed a dense collection of ovoid pleomorphic cells with indented and folded nuclei and variable eosinophilic cytoplasm (Fig. 2). The neoplastic cells showed prominent nuclear atypia in the form of pleomorphism, clumped dense chromatin and variably prominent nucleoli, as well as diffuse and strong expression of S-100 and CD1a consistent with neoplasm of Langerhans cell lineage. However, the presence of highly atypical cytologic findings and high mitotic rate were consistent with LCS. There was variable expression for CD4, LCA and CD68. The neoplastic cells were negative for CD30, CD123, CD21, CD20, CD3, lysozyme, myeloperoxidase, CD34, and CD117. Chromogen in situ hybridization for Epstein-Barr encoding region (EBER) was negative. Mitoses were frequently identified. The Ki-67 proliferative index was approximately 85%. The epidermis was mostly not involved. Surgical margins were free of the tumor. The tumor was staged as T1N0M0. Subsequent molecular testing showed that the tumor was negative for *BRAF* mutations.

5. Treatment

The patient underwent partial right radical vulvectomy with wide local excision of the lesion followed by post-operative adjuvant radiation therapy to the resection bed and ipsilateral perineal tissues, to a total dose of 45.6 Gy; delivered in 38 dose fractions of 1.2 Gy, at 2 fractions per day for 19 total treatment days. The patient completed radiation therapy as planned with no significant adverse acute side effect events.

6. Follow-up

The patient was evaluated by clinical exam every 3 months. A CT scan one year after surgery did not reveal any local or distant disease recurrence. After 33 months of surveillance, the patient remains with no

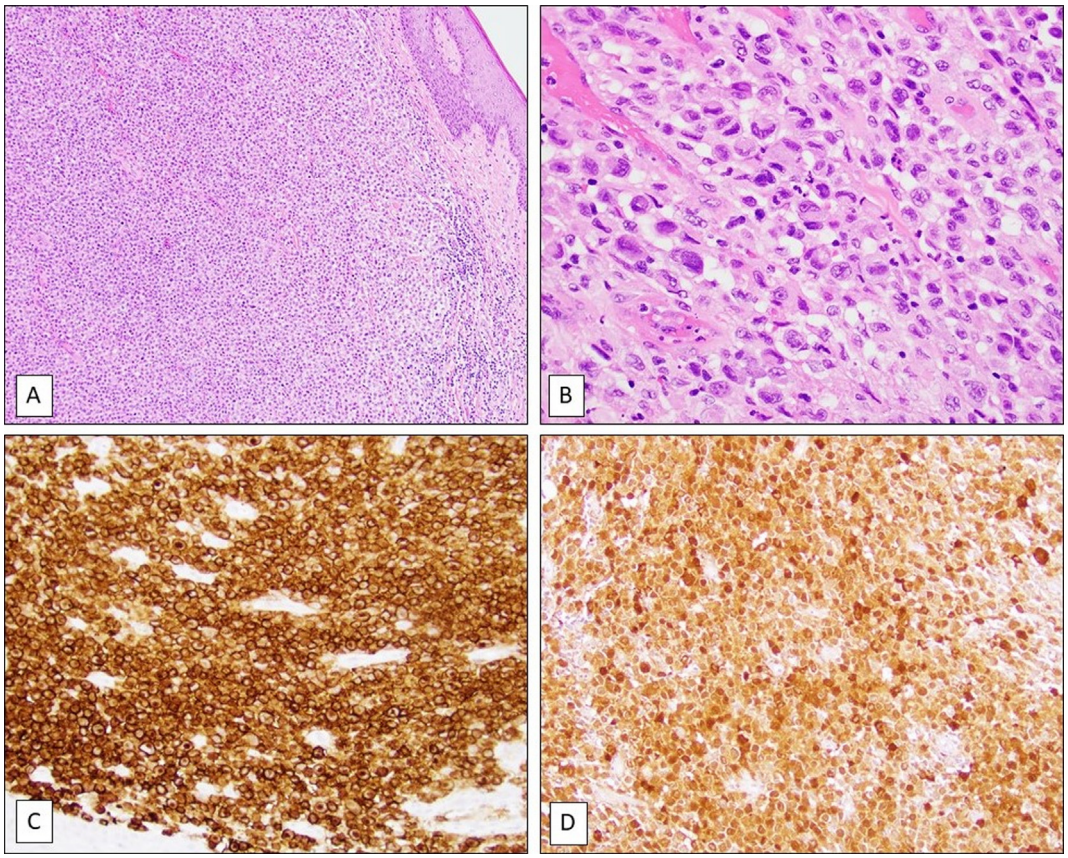

Fig. 2. The histologic sections of the vulvar lesion at lower power (Fig. 2A; 100×) shows dense collection of ovoid cells. At high power (Fig. 2B, 400×), marked nuclear atypia in the form of nuclear pleomorphism, clumped dense chromatin and variably prominent nucleoli is identified. The neoplastic cells show diffuse expression for CD1a (Fig. 2C, 200×) and S100 (Fig. 2D, 200×).

evidence of LCS disease.

7. Discussion

Langerhans cells are dendritic antigen presenting cells that function as part of the immune system. They specifically contribute to the histiocyte system, which is divided into two cellular subsets: phagocytic cells (antigen processing) and dendritic cells (antigen presenting cells). They reside in the supra-basal layers of the dermis, mucous membranes, lymph nodes, and the thymus gland. Langerhans cell tumors are classified by the World Health Organization into two groups: Langerhans cell histiocytosis (LCH) and Langerhans cell sarcoma (LCS). Langerhans cell sarcoma (LCS) is a rare, malignant neoplastic disorder of Langerhans cells thought to arise from antecedent Langerhans cell histiocytosis (LCH), a clinically benign disease, or *de novo* (Howard et al., 2015).

The diagnosis of LCS is based on findings of malignant cytological features as well as the immunophenotype, featuring expression of specific markers such as CD1a, S100, and langerin (CD207) (Yi et al., 2019). In the United States, it is estimated that LCS has an incidence of 0.2 per 10,000,000 population (Tella et al., 2019). According to the most recent systematic review, there are approximately 70 cases of LCS reported in the medical literature (Howard et al., 2015), with this case being the first reported involving the vulva. The most common primary site observed is the skin, followed by the lymph nodes. Metastasis most commonly occurs to lymph nodes, with initial spread occurring via the local lymphatics prior to further dissemination. Other common locations include the lungs. More advanced disease can disseminate to bone marrow, liver, spleen, and kidneys as well (Howard et al., 2015)..

Due to the rarity of this disease, it is evident that the medical literature lack sufficient data to define management guidelines with regard to adjuvant treatment, including radiotherapy and chemotherapy regimens for both localized and systemic LCS. Comparing cases of locoregional LCS across different anatomical locations, there is also inconsistency with regard to surgical intervention and adjuvant treatment. Table 1 aims to demonstrate the lack of consensus that exists regarding management of LCS, specifically in cases where lesions were confined solely to the skin, with examples of some cases from the literature.

A 2019 retrospective reporting of LCS patients diagnosed between 2001 and 2014 supports the current understanding that LCS is extremely rare and often has a poor prognosis. Furthermore, although limited, the study demonstrated that radiotherapy may offer a survival advantage in patients with locoregional disease without bone marrow and reticuloendothelial system involvement (Tella et al., 2019). Our multidisciplinary tumor board suggested adjuvant radiotherapy based on the potential benefits of reducing the risk of recurrence, tolerable side effects and low risk for severe toxicity. Limited data suggests adjuvant chemotherapy and radiation for local or locoregional LCS with adverse features after surgery, such as positive margins, immunosuppression, other hematological disease, and clinical concerns.

8. Conclusion

Langerhans cell sarcoma is a diagnosis associated with a poor prognosis, and perhaps, this is due to the lack of familiarity with the diagnosis, causing delayed identification, as well as a lack of a standard of care for managing this disease. This case report suggests that with localized disease surgical excision followed by radiotherapy may be a reasonable approach for preventing recurrence and metastatic disease. Due to the rarity of LCS, a randomized control trial comparing adjuvant radiotherapy versus chemotherapy may not be done; however, creating a tumor registry may help to assess the role of either or combined approaches. Early recognition and treatment are critical, and this can be accomplished by prompt referral to a specialist as well as establishing a low threshold for biopsy. Further investigation is needed for

Table 1
Summary of cases of Langerhans cell sarcoma with solely skin involvement at diagnosis.

No.	Reference	Site(s) at diagnosis	Treatment(s)	Outcome at Follow Up	Comments
1	Yi et al. (2019)	Right groin	Surgical resection + adjuvant E-CHOP* × 6 cycles	Alive with disease	Arising from antecedent LCH
2	Li et al. (2013)	Ulcerated erythematous plaque on extensor side of right knee	Surgical resection + systemic CHOP** × 6 cycles	Alive with no recurrence	
3	Pileri et al. (2002)	Multiple nodular lesions on skin	N/A	N/A	
4	Pileri et al. (2002)	Single nodular skin lesion	Surgical resection + radiotherapy	Alive with no recurrence	
5	Misery et al. (2003)	Single red, hardened nodular skin lesion on abdomen	Surgical resection	Alive with no recurrence	
6	Sagransky et al. (2013)	Subcutaneous nodules on lower extremities, left abdomen, right forearm	Consolidation chemotherapy with high dose cytarabine × 2 cycles + 3-day low-dose decitabine + allogenic bone marrow transplant	Alive with no recurrence	History of acute myeloid leukemia treated with decitabine, daunorubicin, cytarabine
7	Sagransky et al. (2013)	Nodular scalp lesion	Surgical resection	Alive with no recurrence	Involving papillary and reticular dermis
8	Sagransky et al. (2013)	Eruptive papular violaceous rash	N/A	Died within 3 months of presentation	Concurrent bone marrow biopsy showing myelodysplastic/myeloproliferative process
9	Wang et al. (2012)	Multifocal cutaneous lesions involving bilateral inguinal regions and waist	Surgical resection + cyclophosphamide, oncovin, prednisone × 6 cycles + radiotherapy	Died of metastatic disease	
10	Deng et al. (2008)	Nodular scalp lesion	Surgical resection	Died at 3 months	Past medical history of colon cancer
11	Uchida et al. (2008)	Left upper arm lesion	Neoadjuvant chemotherapy (MAID*** regimen) + surgical resection	Alive with no recurrence	
12	Present case	Right vulvar lesion	Surgical resection + radiotherapy (45.6 Gy)	Alive with no recurrence	

* E-CHOP = etoposide, cyclophosphamide, vindesine, dexamethasone.
** CHOP = cyclophosphamide, doxorubicin, oncovin, prednisone.
*** MAID = mesna, doxorubicin, ifosfamide, dacarbazine.

establishing a standardized treatment for LCS that maximizes the best outcomes.

CRediT authorship contribution statement

Stephanie Tillit: Conceptualization, literature search, medical record review, writing manuscript. **Semiramis Carbajal Mamani:** Conceptualization, literature search, medical record review, original draft. **Robert Zlotecki:** Patient care, medical record review, writing review & editing. **Li-Jun Yang:** Visualization, writing review & editing. **Ashwini Esnakula:** Visualization, writing review & editing. **Jacqueline Castagno:** Patient care, writing review & editing. **Joel Cardenas Goicoechea:** Conceptualization, patient care, medical record review, writing review & editing, formatted the manuscript for submission, acquisition of patient consent.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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