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An Unusual Case of Cutaneous Langerhans Cell Sarcoma Lacking S100 Expression: A Case Report and Review of the Literature

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ABSTRACT

Langerhans cell sarcoma (LCS) is a rare neoplastic proliferation of Langerhans cell with aggressive clinical behavior and involves multiple organ systems, including the skin. LCS is characterized by marked cytologic atypia, frequent mitoses including atypical ones, and expression of CD1a, S100, and langerin (CD207). CD1a and Langerin-positive but S100− negative LCS is extremely rare in clinical practice. We present a case of a 71-year-old female with a history of melanoma and atypical fibroxanthoma who presented with an erythematous plaque on her left knee. Histopathologic examination revealed a dermal infiltrate comprised of large pleomorphic cells with irregular nuclear contours, prominent longitudinal grooves, and vesicular chromatin, and a high mitotic rate. Notably, there were epidermotropism and a distinctive immunohistochemical profile: S100−, CD1a+, Langerin+, and focal CD68+. Next-generation sequencing identified copy number loss of *CDKN2A*, *CDKN2B*, and *FOXA1*, mutations in *TP53*, *POT1*, *SH2B3*, and *SMARCA4*, and a high tumor mutational burden. Herein, we discuss the clinical and pathologic features of 38 cases of LCS with cutaneous involvement reported in the literature, including recent advances in understanding molecular characteristics of this disease. This exceptional case may contribute to our understanding of the etiology of this rare neoplasm.

1 | Introduction

Langerhans cell sarcoma (LCS) is a rare and aggressive neoplasm arising from Langerhans cells (LCs) characterized by malignant cytologic features and poor prognosis [1–3]. LCs are antigen-presenting cells (APCs) present in the suprabasilar layers of the epidermis, lymph nodes, and mucous membranes of various organs. LC tumors are divided into cytologically benign and malignant proliferations, referred to as Langerhans cell histiocytosis (LCH) and LCS, respectively [4–6].

LCS is characterized histologically by pleomorphic, highly malignant cytomorphology, a high mitotic index, and at least partial retention of the LC immunophenotype, including expression of CD1a, langerin, and S100, any of which may be focal [7–9]. Thus, the diagnosis of LCS relies on identifying LC lineage through immunophenotyping or ultrastructural analysis showing Birbeck granules [1, 10]. Given the low frequency and potential diagnostic complexity, it is necessary to differentiate it from other tumors with similar or overlapping features such as metastatic carcinoma/sarcoma, malignant melanoma, anaplastic

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large cell lymphoma, and other histiocytic/dendritic cell neoplasms, including LCH, indeterminate dendritic cell tumor, and interdigitating dendritic cell sarcoma. Therefore, a more thorough understanding of the molecular characteristics of LCS may play a pivotal role in establishing its diagnosis.

While the molecular pathogenesis of this rare disease is poorly understood, recent studies suggest that LCS and LCH may harbor distinct mutational profiles. LCH is characterized by frequent mutations in the MAPK pathway, particularly *BRAF* p.V600E mutations, followed by mutations involving *MAP2K1* [10–13]. In contrast, while there is limited data on the molecular landscape of LCS, it seems to exhibit *CDKN2A/B* deletions and *TP53* mutations instead [10, 14].

Pathogenetically, LCS may arise de novo or as a secondary neoplasm, including as a transdifferentiation event from a prior low-grade B-cell lymphoma and, rarely, as progression from LCH [5]. Several etiological factors for LCS have been proposed, including immunosuppression and viral infection [1, 15]. Treatment options include surgery, radiotherapy, and chemotherapy, but outcomes are generally poor [16]. Further research is needed to improve the understanding, diagnosis, and management of this rare malignancy.

Herein, we report an unusual case of LCS involving the skin characterized by diffuse positivity for CD1a and langerin but negative S100 staining. We also review the current knowledge of this rare disease occurring in the skin.

2 | Case Report

A 71-year-old female with a history of non-small cell lung cancer (Stage III with lymph node involvement) status post chemotherapy and immunotherapy with Keytruda, blood cell dyscrasia (2020, no further details available) melanoma of the right shoulder (2013, breslow depth unknown, did not require lymph node biopsy), and atypical fibroxanthoma of the left lower lateral shin 2 years prior presented with an erythematous plaque on the left knee (Figure 1). Microscopic examination of the lesion revealed an infiltrative neoplasm composed of large pleomorphic cells with irregular, variably reniform nuclear contours, occasional longitudinal grooves, and vesicular chromatin with a moderate amount of grayish cytoplasm involving the dermis and subcutaneous tissue with an overlying grenz zone. Frequent conspicuous and often atypical mitotic figures and necrosis were noted. Occasional neutrophils and rare eosinophils were present superficially, along with a dense subepidermal infiltrate of CD163+ macrophages and numerous admixed CD3+ T-cells in the subcutis (Figure 2).

Immunohistochemical (IHC) stains showed strong expression of CD1a and langerin in lesional cells, along with focal CD68 (paranuclear dot-like). Notably, the tumor cells were negative for S100, as well as CD3, CD20, SOX10, keratin (AE1/AE3), p40, TTF-1, OCT2, cyclin D1, CD163, and CD14 (Figure 3). Next-generation sequencing (performed at Tempus, Chicago, IL) identified a high tumor mutational burden (17.4 m/Mb), pathogenic mutations in *TP53* (*VAF* 32.1%), *POT1* (*VAF* 37.2%), *SH2B3* (*VAF* 59%), and *SMARCA4* (43.2%), and copy number losses involving *CDKN2A/B* and *FOXA1*.

In terms of management, the patient underwent surgical resection of the LCS with clear margins. Although there was a trace of residual atypia in the muscle, it was not significant enough to warrant further excision. The patient continues to undergo active surveillance for the LCS on a biannual basis and receives CT scans every 3 months. Currently, the patient is cancer-free.

2.1 | Comparison to Prior Biopsy

Histologic review of the patient's prior lesion from 2 years prior located a few inches inferior to the current lesion on left lower leg, showed an ulcerated, dermal-based nodular neoplasm with morphology and immunophenotype similar to the current case. The prior neoplasm, however, showed an intraepidermal

FIGURE 1 | Clinical photographs. (A) Current lesion involving the left knee. (B) Previous lesion involving the left lower leg.

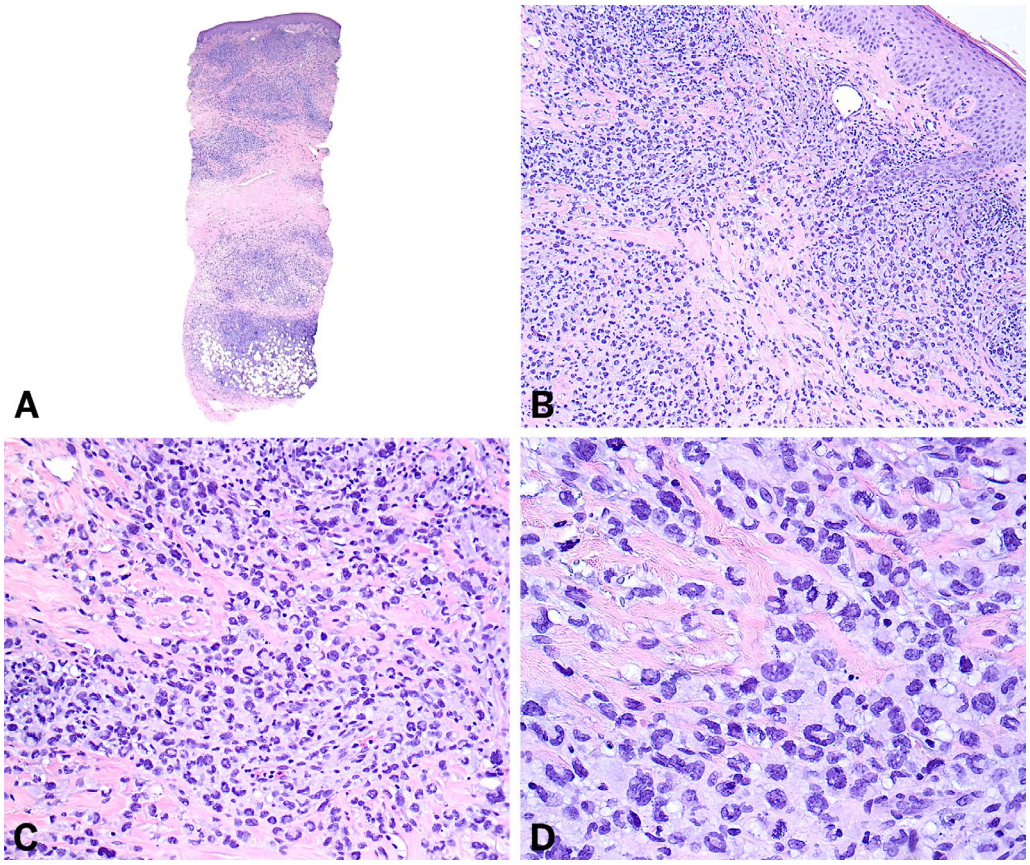

FIGURE 2 | (A–D) Various histomorphologic features of the left knee punch biopsy. (A) Pan-dermal multinodular infiltrate extending into the subcutis (H&E, ×20). (B, C) Sheets of pleomorphic cells with a Grenz zone and intervening bands of fibrosis (H&E, ×100/×200). (D) Malignant cells show variably reniform nuclear contours with moderate grayish cytoplasm and numerous mitotic figures (H&E, ×400).

component. The intraepidermal cells showed marked pagetoid spread with scattered microabscess-like aggregates, as well as a spectrum of cytomorphologic features ranging from frankly malignant to more well-differentiated (Figure 4). Lesional cells were additionally present in the superficial dermis, along with a more conspicuous infiltrate of eosinophils. By IHC, the cells were strongly positive for CD1a and langerin while generally negative for S100, Melan-A, p40, keratin (AE1/AE3), CD10, CD14, CD163, OCT2, CD68, cyclin D1, and PD-L1. The intraepidermal component showed some weak, patchy immunoreactivity for S100, cyclin D1, OCT2, CD14, and CD163. Neither imaging studies nor a bone marrow biopsy were performed.

Given the similar morphologic and IHC features and anatomic location, these neoplasms are likely related with the recent biopsy representing a local recurrence/locoregional spread.

3 | Discussion

We present an unusual case of LCS characterized by negative S100 staining but diffuse positivity for CD1 and langerin. This case is particularly noteworthy due to its morphological similarities to melanoma, including epidermal involvement with pagetosis, in a patient with a prior history of malignant melanoma, posing a significant diagnostic challenge. LCS is an extremely rare entity, with only 57 cases reported in SEER registries from 2000 to 2019. The overall incidence rate is 0.2 per 10000000, showing no significant variations by sex or race. Approximately 40% of cases present with advanced disease. The prognosis for LCS is generally poor, with a 1-year overall survival rate of 63.8% among diagnosed patients in the United States [16, 17]. Most cases occur in extra-nodal sites, such as skin, lung, bone, and soft tissue. Lung, liver, spleen, lymph nodes, and bone are affected in multiorgan disease, with widespread disease occurring in 45% of cases [9]. LCS is difficult to diagnose accurately on H&E staining alone due to clinical and histological similarities to other skin malignancies, hence, immunophenotyping is vital.

Including the present case, we are aware of 38 cases of LCS involving the skin (see Table 1). Twenty cases occurred in male patients, and 18 cases occurred in females (age range: 10–91 years/old; median age: 59). Most LCS patients presented with ulcerated erythematous patches or nodules, commonly involving the lower extremities (seven cases, 18%), sscalp (five cases, 13%), and groin (five cases, 13%). The lesions were either solitary, multifocal, or started as solitary lesions but then progressed to multiple lesions. Fourteen patients (36%) showed exclusively cutaneous disease without involvement of other organs. Lymph nodes were most commonly involved (45% of cases), followed by lung and bone/bone marrow. Spleen and liver involvement were also seen. A single case of breast involvement was reported [4]. Four cases (10%) were associated with other hematolymphoid neoplasms (CLL/SLL, MDS/MPN, AML, hairy cell leukemia). The patients either underwent surgery, received chemotherapy and/or radiotherapy.

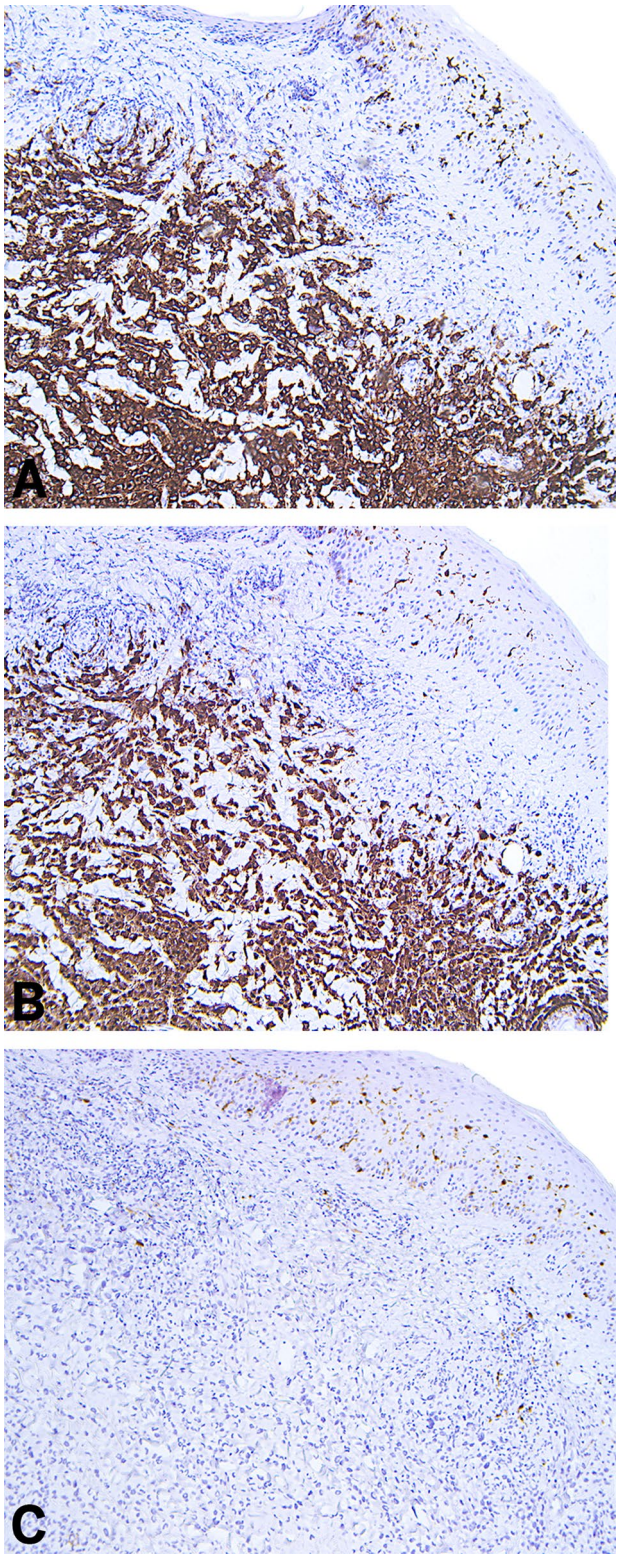

FIGURE 3 | (A–C) Pertinent immunohistochemical stains of the left knee punch biopsy. Lesional cells are diffusely positive for CD1a (A, ×100) and langerin (B, ×100), while negative for S100 (C, ×100). An internal positive control (normal epidermal Langerhans cells) is visible within each image.

Follow-up information was available in 35 cases. Despite treatment, 16 patients (46%) died within 3 years after diagnosis, including 26% ($n = 10$) dying within 1.5 years, indicating that LCS is a highly malignant tumor with a poor prognosis. Of the 14 patients with exclusively cutaneous disease, there was follow-up information for 11 cases. Seven cases achieved complete remission (64%), and three cases died within 1.5 years of diagnosis (27%). The patient in this study is currently alive with disease. This data could indicate a better prognosis for exclusively cutaneous LCS.

On physical exam, 15 cases (39.5%) presented with ulceration. The LCS was composed of large, atypical cells, some with an epithelioid appearance, and pleomorphic nuclei with prominent nucleoli and occasional grooves. The cells were often described as having "bizarre" cytomorphology. Typical LCs and eosinophils were rare or absent. The mitotic rate was high (> 50/10 HPF). Atypical cells were usually found in the dermis and the subcutaneous tissue. In our case, the lesion was comprised of pleomorphic bizarre cells with epidermal involvement. Epidermal involvement was described in 11 (29%) cases analyzed (Table 1). Whether the intraepidermal portion represents an in situ component or epidermotropism is not clear. The presence of ulceration with epidermal involvement highlights the importance of differentiating LCS from melanoma, which has a very similar clinical presentation, especially in patients with a prior history of melanoma.

LCS is reported to express CD1a, S100, and langerin (CD207), in addition to vimentin, cyclin D1, and HLA-DR, with often focal/weak expression of other histiocytic markers, including CD68 and lysozyme. Our case was notably negative for S100 but was diffusely positive for CD1a and langerin. While the lack of S100 expression has been previously described, it appears to be rare. From the cases analyzed in Table 1, only three (8%) had variable/weak S100 [8, 27, 42]; two cases (5%) had weak/negative langerin [5, 25], and two cases (5%) showed weak CD1a [5, 38]. One study reviewed 20 cases and reported only one with complete absence of S100 expression [35]. Furthermore, the International Lymphoma Study Group (ILSG) analyzed 61 suspected histiocytic/dendritic cell tumors using an IHC panel to assess histiocytic (CD68, lysozyme), LC (CD1a, S100), and follicular dendritic cell (CD21, CD35) markers. They found that all LCS cases were positive for CD1a and S100, characteristic of normal LCs. Most LCS cases were positive for CD68 and showed weak lysozyme expression, and were negative for CD21 and CD35, indicating that LCS cases were identifiable only by CD1a expression or ultrastructural Birbeck granules [18]. CD45 was variably expressed in 43% ($n = 4$) of cases. MPO, CD30, CD34, pan-B-cell (CD20, CD79a), and pan-T-cell (CD3) antigens were always negative. The Ki-67 had a mean value of 22.5% in the LCS cases. Another study reported 4 cases expressing CD56, whose presence has been linked to poorer prognosis in certain types of lymphoma; however, CD56 positivity was not seen in any other reported LCS cases analyzed [43]. Two studies proposed that IGF2BP3 expression can help distinguish LCS from LCH in adult patients [18, 44]. Possible explanations for S100 negativity in our case include an aberrant maturation of histiocytes. Additionally, our case showed focal positivity for cyclin D1, which may indicate MAPK pathway activation [10, 18]. The CD3 positivity at the periphery of the tumor could indicate a host-response to the tumor. Our case highlights several unique features of cutaneous LCS, including large atypical pleomorphic cells with epidermal involvement, a dermal inflammatory response, and

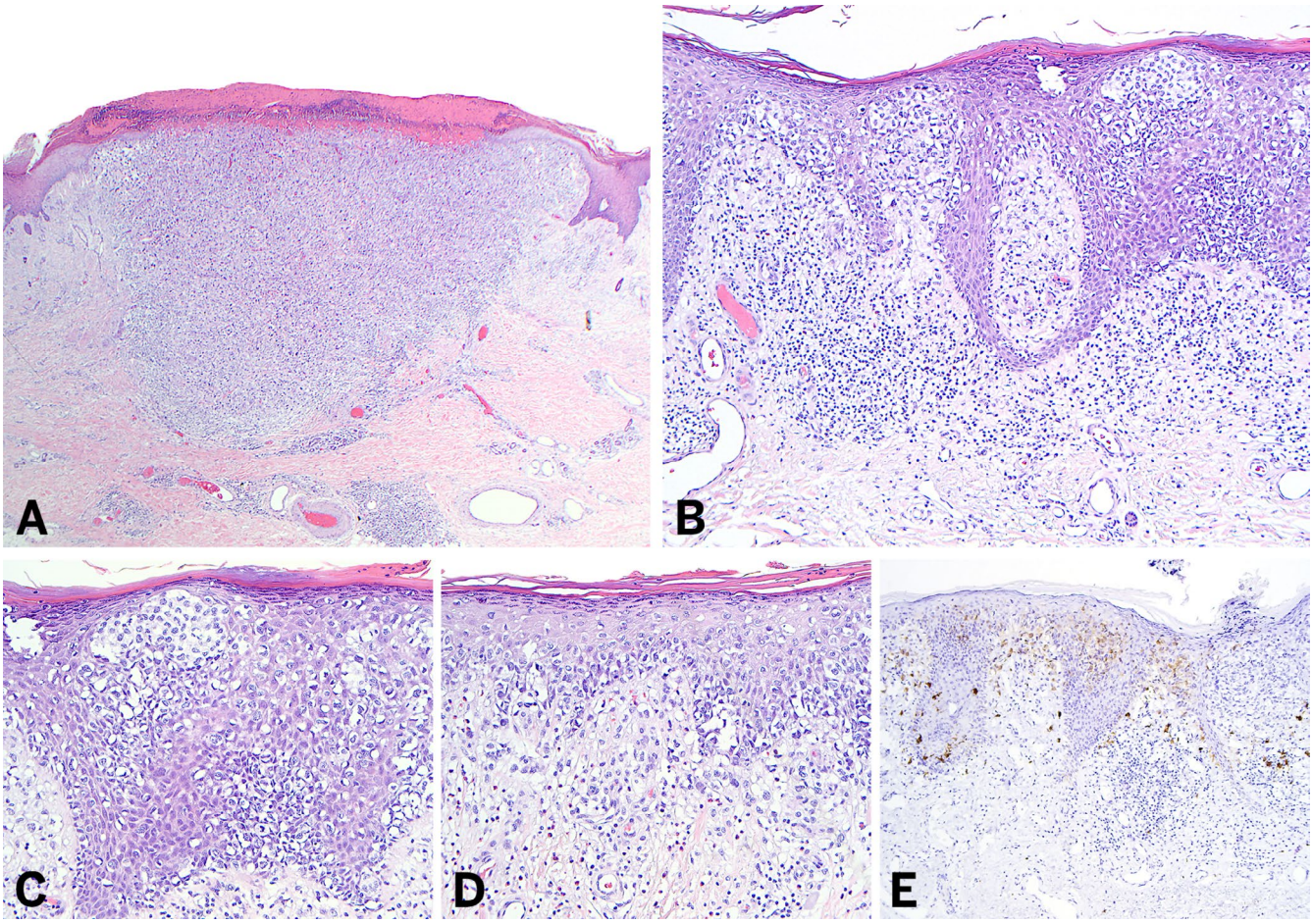

FIGURE 4 | (A–E) Various histomorphologic features of the left leg excision. (A) Nodular, infiltrative growth extending into the mid-to-deep dermis with overlying ulceration and an epidermal collarette (H&E, ×20). (B–D) Adjacent areas show predominantly intraepidermal growth with marked pagetosis and a spectrum of cytomorphologic features, ranging from frankly malignant to more well-differentiated Langerhans cells, including some coalescing into microabscess-like aggregates. Dermal eosinophils are prominent in the final image (H&E, ×100/×200/×200). (E) S100 IHC shows patchy, weak staining of intraepidermal neoplastic cells (compare to strongly staining positive internal control; ×200).

negative S100 with focal CD68 staining, potentially confounding the diagnosis if a limited panel of antibodies is used. The presentation as a plaque may be related to the presence of an intraepidermal component.

It has been previously reported that LCS and LCH show distinct mutational profiles. Whereas LCS has been shown to harbor activating mutations in the MAPK pathway in a subset of cases, it more commonly shows *CDKN2A*/*B* deletions and *TP53* mutations. Mutations in *MAP2K1*, *KRAS*, *NRAS*, *KMT2D*, and *NOTCH1* have been reported; however, few LCS cases harbor *BRAF* mutations. In contrast, LCH frequently shows *BRAF* p.V600E or *MAP2K1* mutations but lacks RAS family and *NOTCH1* mutations and *CDKN2A*/*B* deletions [10, 13, 29, 45]. Our case further affirms these findings, as it showed *CDKN2A*/*B* deletions and *TP53* mutations, along with additional mutations in *POT1*, *SH2B3*, *SMARCA4*, and *FOXA1*, and a high tumor mutational burden. No *BRAF* mutation was detected.

Of the 38 cases included in our review, only 11 cases underwent molecular testing, including 5 tested only *for BRAF* mutations. None of the LCS cases carried *BRAF* mutations. Three cases showed deletions in *CDKN2A* (6q, 9p) and *TP53* mutations similar to the current case [21, 29]. One of these studies also reported *KRAS* p.Q61H mutations [29], and another one reported *KMT2D* p.R3703X and *STK19* p.G265A mutations [21]. One case demonstrated immunoglobulin heavy chain and kappa light chain rearrangements in a patient with underlying hairy cell leukemia [33], and one case detected a clonal proliferation (non-random X inactivation pattern) of LCs [39]. The cases that harbored clonal heavy/light chain gene rearrangements were found in patients with an underlying lymphoma, possibly explained by a transdifferentiation phenomenon. Some LCS cases showed high mutational burdens and UV-associated signatures, suggesting UV involvement in pathogenesis [21]. Another study performed whole genome sequencing and revealed a complex karyotype with variable hyperdiploidy and numerous allelic imbalances, indicating genomic instability [29]. These findings provide insights into LCS pathogenesis and point to potential therapeutic targets while highlighting the importance of comprehensive genetic testing, as targeted *BRAF* testing alone may miss key mutations.

We favor that our case likely represents *de novo* pathogenesis. While aggregates of more well-differentiated and recognizable LCs were identified within the epidermis of the chronologically

TABLE 1 | Previously reported cases of Langerhans cell sarcoma involving the skin.

Year	Author	Age/sex	Clinical presentation	Other organs involved	History of hematolymphoid disorders	Epidermal involvement	IHC staining profile	Genomic alterations	Follow-up
2022/2024	Current case	71/F	Erythematous plaque—knee	No	No	Yes	(+): CD1a, langerin, cyclin D1 (focal), CD68 (focal) Ki67 PI: 60%–70% (−): S100, PDL-1, CD3, CD20, SOX10, CK AE1/AE3, p40, TTF-1, Oct-2, CD163, CD14	LOF: *TP53, POT1, SH2B3, SMARCA4*, CNL: *CDKN2A, CDKN2B*, and *FOXA1* TMB: high (17.4 m/MB)	AWD
			Ulcerated nodule—lower leg	No	No	Yes	(+): CD1a, langerin (−): S100, cyclin D1, CD68, melanA, PDL-1, CD10, CD14, CD163, SOX10, CK AE1/AE3, p40, TTF-1, Oct-2		
2022	Xie et al. [18]	18/M	Flat, firm, mound-shaped lump with clear borders—forehead, 3 cm	Frontal bone, dura	No	No	(+): CD1a, S100, CD68, p53, cyclin D1, cyclin A, cyclin B1, IGF2BP3 Ki67 PI: 45%–50% (−): N/A	N/A	ACR, 1 year
2020	Ronen et al. [7]	62/M	Multiple erythematous papules and scaly areas—face, neck, arms, chest, abdomen, and legs	Lymph nodes	No	Yes	(+): S100, CD1a, langerin, PD-L1 (focal, 10% of cells), cyclin D1 (focal, scattered) Ki67 PI: 60%–70% (−): BRAF V600E, HMB45, melan-A, tyrosinase, SOX10, pankeratin cocktail, CD117, CD30	*BRAF* mutation analysis: negative	AWD
2020	Tillit et al. [19]	73/F	Ulcerated lesion-right labia majora, 2 cm	No	No	No	(+): S100, CD1a, CD4 (variable), LCA (variable), CD68 (variable) Ki67 PI: 85% (−): CD30, CD123, CD21, CD20, CD3, lysozyme, MPO, CD34, CD117	*BRAF* mutation analysis: negative	ACR, 33 months
2020	Papoudou-Bai et al. [20]	60/F	Multiple well-defined reddish firm cutaneous lesions—head, neck, torso	N/A	CLL/SLL	No	(+): CD1a, langerin, S100 Ki67 PI: > 50% (−): CD56, CD21, CD35, CD123, HMB45, pan-cytokeratin	*BRAF* mutation analysis: negative	DOD, 3 years

(Continues)

TABLE 1 | (Continued)

Year	Author	Age/sex	Clinical presentation	Other organs involved	History of hematolymphoid disorders	Epidermal involvement	IHC staining profile	Genomic alterations	Follow-up
2020	Katsuragawa et al. [21]	70/M	Irregular multinodular white tumor-scalp, 3 cm	Lung	No	N/A	(+): S100, CD1a, CD4, CD68, langerin, p53, EZH2, PD-L1 (variable) Ki67 PI: 50% (–): BRAF V600E, p16, CD21, CD23, CD123, CD163, MCPyV, SOX10	SNV/indels: *TP53 (Y88C), KMT2D (R3703X), STK19 (G265A)* Homozygous deletion: 6q, 9p (*CDKN2A*) TMB: high (> 20.31 m/MB) UV-mutational signature	AWD
2019	Yi et al. [22]	41/M	Mass—groin	Lymph nodes	No	N/A	(+): S100, CD1a, Langerin, CD4, CD163, CD68, vimentin Ki67 PI: 65% (–): ALK, HMB45, melan-A, CD3, CD5, CD20, CD30, MUM-1	N/A	AWD
2018	Matsukawa et al. [23]	79/M	Systemic papules	No	No	No	(+): S100, CD1a, CD4, CD56, CD45RO, TIA-1, CD68 (patchy) (–): CD3, CD8, CD30, ALK, granzyme B, EBER, langerin, CD20	N/A	ACR, 23 months
2017	Kwon et al. [24]	35/F	Single erythematous, ulcerated, pustular dome shaped mass—left shin, 2 cm	No	No	Yes	(+): S100, CD1a Ki67 PI: High (not quantitated) (–): CD21, CD 23, HMB-45, melan-A, CK20, SMA	N/A	N/A
2017	Singh et al. [8]	91/M	Ulcerated plaques—back, 3 cm	No	No	Yes	(+): CD1a, Langerin *Variable S100 & CD45 from 3 biopsies of same lesion: (a) S100: + (diffuse); CD45: equivocal (b) S100: + (weak); CD45: equivocal (c) S100: – (negative); CD45: + (diffuse) Ki67 PI: 50%–50% (–): MPO, CD21, CD68, CD20, CD3, CD30, CD15, Alk1, CD2, CD7, CD5, CD56, HMB45, Melan A	N/A	ACR, 24 months

(Continues)

TABLE 1 | (Continued)

Year	Author	Age/sex	Clinical presentation	Other organs involved	History of hematolymphoid disorders	Epidermal involvement	IHC staining profile	Genomic alterations	Follow-up
2017	Soler et al. [25]	66/F	Reddish papule with underlying nodule—anterior lower leg, 3 cm	No	No	Yes	(+): S100, CD1a, CD68, CD4, CD45. CD30, CD3, **Variable Langerin staining: (+) expression in superficial component; (–) in deep aspect of lesion Ki PI: N/A (–): Melanocytic, B-cell lymphocytic, and epithelial markers	*BRAF* mutation analysis: negative No beta or gamma T-cell receptor monoclonality detected	N/A
2016	Zhang et al. [26]	75/M	Firm mass—left knee, 3 cm	Lymph nodes, liver, omentum	No	No	(+): S100, CD1a, CD68, vimentin Ki67 PI: 70% (–): Desmin, CD30, CD15, Actin, HMB-45, melan-A, myoglobin	N/A	DOD, 2 years
2016	Castro-González et al. [4]	81/F	Erythematous indurated plaque—periareolar skin	Breast, lymph nodes	No	No	(+): CD1a, CD4, S100, langerin Ki67 PI: N/A (–): N/A	N/A	DOD, 9 months
2016	Gagnon et al. [27]	70/M	Confluent brown-yellow to violaceous, purpuric, macularand papular eruption—legs, arm, lower abdomen, back	No	No	No	(+): CD1a, CD56, CD31, Fli-1 *Variable positivity: S100, CD45RO, CD43, CD5, CD4 Ki67 PI: N/A (–): Langerin, CD68, CD123, CD34, Factor VIII, Ulex, CD2, CD3, CD7, CD8, TdT	*BRAF* mutation analysis: negative	DOD, 1.5 years
2016	Ma et al. [28]	56/F	Well-demarcated, erythematous, and ulcerated plaques—nose, axilla and groin	Bone, lymph nodes	No	N/A	(+): S100, CD68, CD1a Ki67 PI: N/A (–): N/A	N/A	DOD, 10 days
2015	Karai et al. [29]	62/F	Enlarging excoriated nodule surrounded by smaller satellite lesions—forehead	Lymph nodes	No	Yes	(+): S100, CD1a, langerin, CD4, CD30 (membranous), CD2, CD3, CD43, fascin Ki67 PI: N/A (–): Pan-melanoma cocktail (melan-A, HMB-45, Tyrosinase, CK AE1/AE3)	Homozygous deletion: *CDKN2A* LOH:17p (*TP53* gene) SNVs/indels: *KRAS (Q61H)*, *TP53 (R282W)* No *BRAF* mutations detected Complex karyotype with variable hyper diploidy	DOD, 2 years

(Continues)

TABLE 1 | (Continued)

Year	Author	Age/sex	Clinical presentation	Other organs involved	History of hematolymphoid disorders	Epidermal involvement	IHC staining profile	Genomic alterations	Follow-up
2015	Kwong [30]	24/M	Enlarging mass—groin, 5 cm	Lymph nodes	No	N/A	(+): CD1a, CD4, langerin, and S100 Ki67 PI: N/A (−): N/A	N/A	ACR
2015	Jimura et al. [31]	87/F	Ulcerated, fist-sized, irregularly shaped tumor—groin	No	No	N/A	(+): CD1a, S100 protein Ki67 PI: 40% (−): N/A	N/A	ACR, 8 months
2014	Lee et al. [32]	45/F	Multiple, erythematous plaques with erosions and crust—scalp, axilla	Lymph nodes, lung	No	No	(+): CD1a, CD45, S100, CD68 Ki67 PI: N/A (−): N/A	N/A	APR, 16 months
2013	Li et al. [2]	48/M	Enlarging ulcerated erythematousplaque	No	No	Yes—ulceration only; no epidermotr-opism	(+): S100, CD1a, langerin, CD68 Ki67 PI: 80% (−): CD3, CD5, CD20, CD21, CD30, CD38, CD56, CD79a, ALK, HMB-45, melan-A, pan-cytokeratin, MPO	N/A	ACR, 12 months
2013	Sagransky et al. [5]	54/M	Progressive eruption of tender subcutaneous nodules—lower extremities, left abdomen, and right forearm	No	AML	No	(+): S100, CD1a, CD4, CD34, CD68, CD 83 CD31, MPO, lysozyme Ki67 PI: N/A (−): **Langerin, CD56	N/A	ACR
		63/F	Eruptive papular violaceous rash—lower extremity	No	MD/MP neoplasm, unclassifiable	Yes	(+): CD1a, S100, CD4 Ki67 PI: N/A (−): CD117, CD15, CD34, TdT, CD3, PAX5, lysozyme, CD56, MPO	N/A	DOD, 3 months
		61/M	Protuberant ulcerated nodule—scalp, 2 cm	No	No	Yes—ulceration only; no epidermotr-opism	(+): S100, CD1a (weak), langerin (equivocal), CD4 (weak) KI67 PI: N/A (−): Melan-A, CD56, HMB-45, PGP9.5	N/A	ACR
		88/M	Pearly tan dome, shaped papule with ill-defined violaceous patch-temporal scalp, 0.6 cm	No	No	N/A	(+): S100, CD1a Ki67 PI: N/A (−): HMB-45, melan-A, cytokeratin, CD30	N/A	DOD, 3 months

(Continues)

TABLE 1 | (Continued)

Year	Author	Age/sex	Clinical presentation	Other organs involved	History of hematolymphoid disorders	Epidermal involvement	IHC staining profile	Genomic alterations	Follow-up
2013	Valentín-Nogueras et al. [6]	71/M	Multiple erythematous ulcerated nodules and purpuric macules—scalp, face, trunk, extremities	Lymph nodes	No	No	(+): S100, CD1a Ki67 PI: N/A (–): CKAE1/AE3, CK5/6, CK7, CK20, CKHMW, EMA, CEA, CD31, CD34, vimentin, CD21, TTF-1, HMB-45, melan-A	N/A	DOD, 20 months
2012	Furmanczyk et al. [33]	75/M	Dense black ulcerated nodule with surrounding erythema-right forearm, 1 cm 5 months later: soft tissue nodule resembling hematoma—forearm + splenomegaly (soft tissue + splenic biopsies taken)	Spleen	Hairy cell leukemia	Yes—ulceration only; no epidermotropism	(+): S100, CD1a, langerin Ki67 PI: N/A (–): B-cell markers (CD20, Pax5, CD79a, kappa and lambda), melanocytic markers (Melan-A, HMB45 and tyrosinase), T-cell markers (CD3 and CD30), epithelial markers (AE1/AE3), markers associated with hairy cell leukemia (CD25 and DBA44) Subcutaneous nodule: same as above Spleen-2 populations found: (a) (+): S100, CD45 Ki67 PI: N/A (–): CD1a, B-cell markers (CD20 and CD79a), hairy cell marker (CD25), bcl-6, cyclin-D1, CD3, CD10, CD23, CD1a (b) background small B-cells with abnormal expression of CD11c, CD19, CD20, CD103	Immunoglobulin heavy chain and kappa light chain rearrangements	DOD, 13 months
2012	Wang et al. [3]	41/M	Multiple primary foci: (a) tender soft tissue mass—left waist, 10 cm; recurred as a cordlike tissue with a sharp border s/p resection (b) slow-growing painless mass—left groin, 15 cm (c) painless mass, right groin, 6 cm	Liver, lung	No	No	(+): CD1a, langerin, S100, CD68, vimentin, lysozyme (weak) Ki67 PI: 70%–90% (–): follicular dendritic cell markers (CD23, CD35), pan-T or B cell markers [CD45 (LCA), CD20, CD3, CD30], epithelial markers (AE1/AE3), CD56, ALK, CD138, PAX-5, CD15, MPO	N/A	DOD, < 1 year

(Continues)

TABLE 1 | (Continued)

Year	Author	Age/sex	Clinical presentation	Other organs involved	History of hematolymphoid disorders	Epidermal involvement	IHC staining profile	Genomic alterations	Follow-up
2008	Deng et al. [34]	88/M	Rapidly growing, slightly scaly erythematous nodule on an ill-defined violaceous patch—scalp, 1.9 cm	No	No	No	(+): S100, CD1a Focal positivity: CD45rb, CD68, CD163, CD83, lysozyme (−): HMB-45, melan-A, pan-cytokeratin, CD3, CD20, CD21, CD30	N/A	DOD, 3 months
2007	Bohn et al. [35]	47/M	Slow growing, ulcerated mass—scalp	Lymph nodes	No	No	(+): CD1a, CD68, S100, langerin (CD207), vimentin, p53 (overexpression) Ki67 PI: 60%–90% (−): T-cell antigens (CD3, CD5), pan–B-cell antigens (CD20, CD79a), CD21, CD30, CD35, CD43, CD56, CD45RO, ALK, EMA, CK AE1/3, melan-A	N/A	AWD, 18 months
2007	Diaz-Sarrio et al. [36]	58/M	Indurated erythematous asymptomatic mass with adjacent nodules—7 cm, abdomen	Lymph nodes	No	Yes (ulceration only; no epidermotropism)	(+): S100, CD1a, vimentin Ki67 PI: N/A (−): CK 7, CK 20, desmin, CD68, CD34, melan-A	N/A	AWD, 6 months
2006	Ferringer et al. [37]	33/F	Rapidly enlarging firm erythematous tumor—posterior thigh, 3 cm	Lymph nodes	No	Yes	(+): S100, CD1a, NSE, CD31 Ki67 PI: N/A (−): MART-1, HMB-45, AE1/AE3 pan-keratin, CD45, CD3, CD20, CD68, chromogranin, MPO, CD99, BerH2	N/A	ACR, 8 months
2002	Pileri et al. [38]	50/F	Multiple nodules	No	No	N/A	(+): S100, CD68, lysozyme, CD1a (weak), CD45 (weak) Ki67 PI: 60% (−): CD21 CD35, MPO, CD3, CD20, CD79a, CD30	N/A	N/A
		10/F	Single nodule	No	No	N/A	(+): CD68, Lysozyme, S100, CD1a (patchy) Ki67 PI: 8% (−): CD21 CD35, MPO, CD45, CD3, CD20, CD79a, CD30	N/A	ACR

(Continues)

TABLE 1 | (Continued)

Year	Author	Age/sex	Clinical presentation	Other organs involved	History of hematolymphoid disorders	Epidermal involvement	IHC staining profile	Genomic alterations	Follow-up
		23/F	N/A	Lymph nodes, lung	No	N/A	(+): S100, CD68(+/−); lysozyme (rare) Ki67 PI: N/A (−): CD21 CD35, MPO, CD45, CD3, CD20, CD79a, CD30	N/A	DOD
2001	Itoh et al. [39]	74/F	Ulceratederythematous plaque-right hand	Lymph nodes	No	Yes	(+): S100, CD1a, vimentin Ki67 PI: 20% (−): CD68, lysozyme, HAM-56, neurofilament, HMB-45, melan-A, cytokeratin, EMA, CD20, CD 30, CD45, CD4, CD79a, desmin	HUMARA assay: clonal proliferation detected (non-random X inactivation pattern)	DOD, 14 months
1994	Lauritzen et al. [40]	38/M	Skin, not specified	Lymph nodes, lung	No	No	(+): S100, CD1a, CD68, lysozyme, p53, CD11b, CD 11c, CD13, CD 14 Ki67 PI: N/A (−): CD33, CD34, CD45, L1 antigen, R4/23, PNA	N/A	P, 12 months
1991	Delabie et al. [41]	23/F	Multiple flesh-colored nodules—leg, trunk, face	Lymph nodes. Liver, lung	No	Yes	(+): S100, adenosine triphosphatase, CD68, vimentin, alpha-1-anti-chymotrypsin, CD11b (patchy), CD14 (patchy), EMA (focal), HLA-DR (focal) Ki 67 PI: N/A (−): CD1a, lysozyme, CD30, CD45, IL2, B-cell markers, T-cell markers, cytokeratins	Immunoglobulin and T-cell receptor genes: no clonal proliferation identified (germ-line configuration)	DOD, 2 months
1992	Tani et al. [42]	49/F	Dark-red ulcerated plaque-extensor surface, left leg, 5.2 cm	Lymph nodes, bone marrow, liver, lungs, kidney	No	Yes	(+): CD1a Focally positive: HLA-UR, CD2, CD3, CD4, CD8, CDllb, CD21 Ki67 PI: N/A (−): *S100, lysozyme. Factor XIIIa, immunoglobulins	N/A	DOD, 12 months

Abbreviations: ACR, alive in complete remission; APR, alive with partial remission; AWD, alive with disease; CK, cytokeratin; CNL, Copy number loss; CR, complete remission; DOD, died of disease; F, female; LOF, loss of function mutational variants; M, male; MPO, myeloperoxidase; NA, not available; NSE, neuron specific enolase; P, partial remission; PI, proliferation index; PNA, peanut agglutinin; TMB, tumor mutational burden; WES, whole-exome sequencing; *cases with variable/negative S100; **cases with variable/negative langerin.

earlier excision, a discrete cytologically benign population co-expressing S100 was not identified. Additionally, no MAPK pathway driver mutation was detected, and the patient did not have a previous diagnosis of lymphoma or LCH, arguing against progression from a precursor neoplasm. In fact, de novo tumorigenesis appears to be the most common pathway in LCS based on literature review, with a minority of cases reported as arising from a low-grade B-cell lymphoma (and sharing clonally related immunoglobulin gene rearrangements). Very rare, isolated case reports exist detailing LCS arising in association with, or as progression from, LCH [25, 46]. Additionally, while LCH is not defined by the presence of *BRAF* p.V600E or other MAPK driver mutation, the vast majority do harbor one of these [9, 47]. In contrast, these mutations appear to be relatively uncommon in cutaneous lesions of LCS. Thus, progression from a precursor LCH to LCS may be a rare event, although additional studies are needed to confirm this.

LCS is a rare, aggressive neoplasm with poor outcomes. A thorough analysis of molecular, genetic, and clinical features is crucial to develop improved diagnostic algorithms and targeted therapy with a goal of improving prognosis. The variability of immunophenotype, including lack of S100 expression seen in this case, highlights the potential diagnostic challenges. Further research is needed to improve the understanding and management of this rare malignancy.

Ethics Statement

Institutional Review Board approval was obtained from Indiana University, IN, USA.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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