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Case series

Langerhans cell histiocytosis limited to the female genital tract: A review of literature with three additional cases

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1. Introduction

Langerhans cell histiocytosis (LCH) is a tumor composed of a proliferation, usually clonal, of cells sharing morphologic and immunophenotypic characteristics with skin Langerhans cells, and is classified amongst other histiocytic and dendritic cell neoplasms (Cancer, 2008). Presentation can vary from single organ involvement to disseminated, multi-system disease. Clinical aggressiveness is equally variable. In 1939 Andrews first described LCH of the female reproductive tract, subsequently four patterns of involvement have been identified: (a) pure genital LCH, (b) genital tract LCH with subsequent multi-organ involvement, (c) oral or cutaneous LCH with subsequent genital and multi-organ involvement, and (d) diabetes insipidus with organ involvement (Axiotis et al., 1991). Sites include the vulva, vagina, cervix and endometrium, with vulva being the most common site. A comprehensive literature review revealed 35 cases of pure genital LCH. We report two new cases of solitary LCH lesions involving the vulva and one involving the cervix to the literature.

2. Case 1

GH is a 26 year old female who presented in May of 2015 with vulvar pruritis and a painful vulvar lesion for 4 days. On history she denied thirst, skin rash, headaches, bone pain, or hearing loss. Her medical history was notable for a history of chlamydia and she was a current smoker. On clinical examination a 2 mm pruritic and painful raised papule on the left labia minora was noted. Herpes simplex virus (HSV) collection was performed and the patient was empirically started on Valcyclovir. HSV results returned negative and Valcyclovir was discontinued. A vulvar biopsy was performed two weeks after initial presentation and confirmed LCH. The patient was referred to a medical oncologist who performed a complete systemic workup.

The pathologic specimen revealed a nodular collection of reniform Langerhans cells associated with an eosinophilic-rich inflammatory infiltrate (Fig. 1a, b). The Langerhans cells demonstrated CD1a (clone) and S100 (clone) immunoreactivity (Fig. 1c, d) The patient was referred to a gynecologic oncologist for consideration of a larger surgical excision. However, the lesion had been completely excised following the biopsy, and no additional surgery was performed. She was placed into surveillance per the National Comprehensive Cancer Network (NCCN) guidelines, with follow-up planned every 3–6 months for 2 years, then 6–12 months for 3–5 years and then annually. The patient remains disease free for 23 months.

3. Case 2

BM is a 67 year old female who presented in June 2006 with a pruritic vesicle at 1 o'clock on her left labia majora for an unspecified amount of time. Her past medical history is significant for combined urge and stress incontinence, eczema, hypertension, hyperlipidemia, arthritis, diabetes mellitus type 2, and polymyalgia rheumatic. Clinical examination was normal except for a small vesicle on the left labia majora. An HSV culture was negative. She failed treatment with a topical steroid and the persistent raised pruritic lesion was then biopsied

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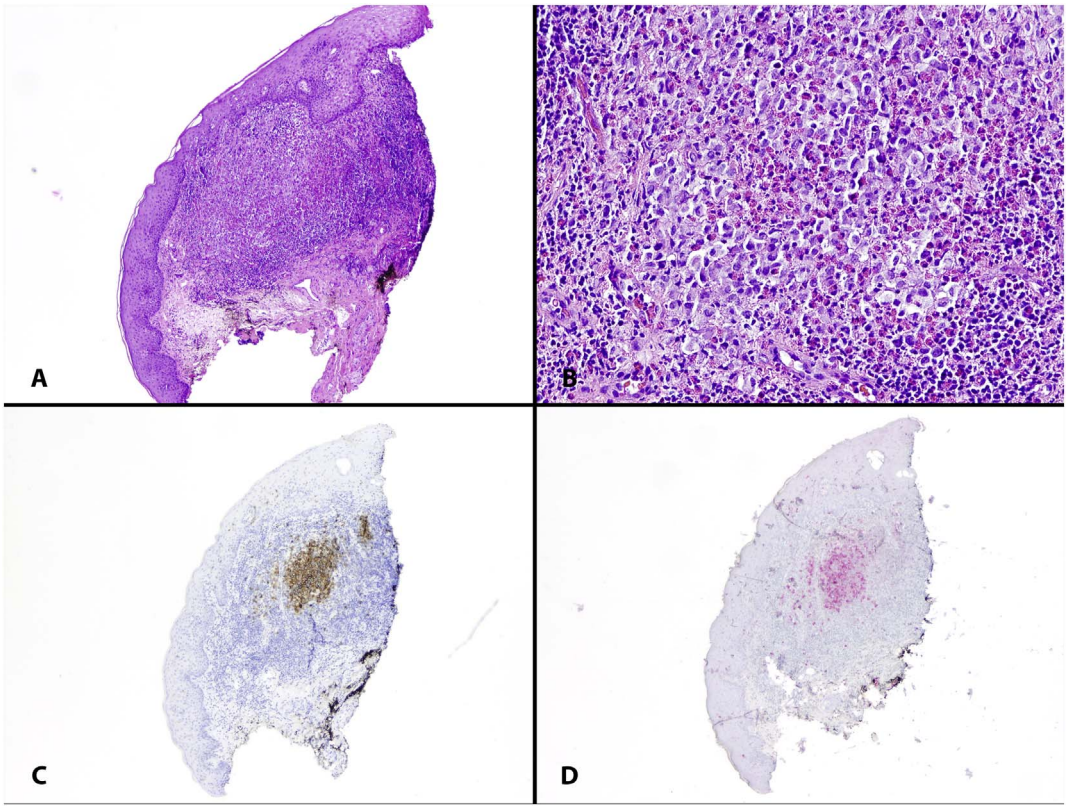

Fig. 1. (a) Low power of vulva depicting lesion. Hematoxylin and eosin stain, 40 × (b) histiocytes and eosinophils within lesion, 200 ×, immunohistochemical staining of neoplastic LCH cells, magnification 40 ×. (c) CD1a cytoplasmic staining, (d) S100 nuclear and cytoplasmic staining.

four weeks after initial presentation to clinic.

The pathologic specimen demonstrated increased epidermal and dermal Langerhans cells with Langerhans cell microabscess formation. The Langerhans cells were immunoreactive for CD1a (Dako, 010 clone). Additionally, there was a superficial dermal inflammatory infiltrate containing lymphocytes and eosinophils. Unlike Case #1, this patient did not undergo a systemic workup, nor was she entered into clinical surveillance per the NCCN guidelines due to loss to follow up. She later presented with lichen simplex chronicus (LSC) on her neck, waistline and antecubital fossa. Clinical examination revealed intact genital anatomy with no atrophy or erosions, mild lichenification, and atopic dermatosisis with LSC. At this time she was encouraged to apply hydrocortisone cream for the treatment of LSC. The patient remains disease free from her LCH for 10 years, 10 months.

4. Case 3

AR is a 31 year-old woman with Hepatitis C, history of intravenous drug use, smoking and an extensive history of cervical dysplasia for over a decade. She presented in 2012 for colposcopy following a Pap smear revealing a high-grade squamous intraepithelial lesion (HSIL).

A biopsy performed during the colposcopy demonstrated a collection of cells in the dermis with Langerhans morphology, which were immunoreactive for CD1a (Leica, MTB1 clone) and S100 (Ventana, 4C4.9 clone) (Fig. 2a–d). Gynecological examination revealed copious discharge from the vagina and a multiparous, shortened cervix due to prior loop electrosurgical excision procedure (LEEP) with an otherwise normal exam. At this time the patient complained of polydipsia and polyuria, some memory difficulties, a rash on her chest, some lesions of the left lower extremity and knee, fatigue, weight loss, fevers and a nonproductive cough; all of which were suspicious for a multisystemic process. Physical exam revealed a resolving rash on her chest with small raised, red flaky, eczematous lesions, and a small resolving red lesion on left knee with no other notable findings. No biopsy was performed of the skin due to its quick resolution. A hematology oncology consult and full metastatic evaluation including extensive blood work, imaging (full body PET CT, head MRI) and a bone marrow biopsy were negative. It is unclear why she had these concurrent symptoms, but due to the extensive testing it is unlikely that it was due to LCH. Given the possible malignant nature of LCH, a simple hysterectomy was performed for local control. The tumor was 1.2 cm wide × 0.12 cm deep and was localized to the cervix without involvement of the endometrium or uterine body (Fig. 3a,b). No adjuvant treatment was recommended and the patient was entered into surveillance according to the NCCN guidelines. The patient remains disease free from her LCH for 54 months.

5. Discussion

Histiocytes belong to the monocyte-macrophage lineage, a family which includes most types of dendritic cells. The latter are cells specialized in antigen presentation and play an important role within both the innate and adaptive immune responses. Langerhans cells, in turn, are a special type of dendritic cell, resident within the skin, with the capacity for antigen uptake and subsequent migration to draining lymph nodes for antigen presentation to antigen-specific B and T cells (Badalian-Very et al., 2013). LCH was first known as “Histiocytosis X”, and has previously been described as Hand-Sculler-Christian disease (chronic disease characterized by triad of diabetes insipidus, exophthalmos and multifocal lytic bone lesions), Letterer-Siwe's disease (acute dissemination with multisystem involvement), and eosinophilic granuloma (benign form restricted to one organ), depending on clinical manifestation (Lichtenstein, 1953). Such names, however, are now considered historical and should be replaced by LCH (Broadbent et al., 1994).

Until recently, LCH was difficult to differentiate from other

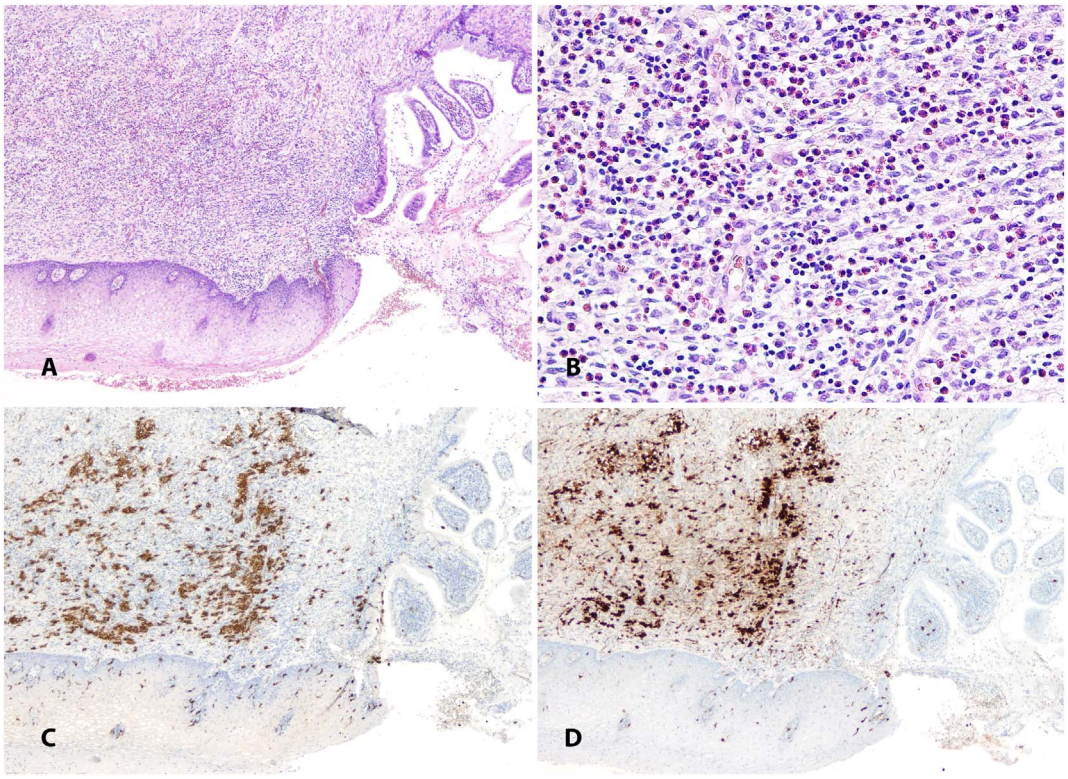

Fig. 2. (a) Low power of cervix transition zone depicting lesion. Hematoxylin and eosin stain, 40 × (b) histiocytes and eosinophils within lesion, immunohistochemical staining of neoplastic LCH cells, magnification 40 ×. (c) CD1a cytoplasmic staining, (d) S100 nuclear and cytoplasmic staining.

hematologic and lymphoid tumors, and still little is known about the true incidence and epidemiologic characteristics of LCH. Although LCH is diagnosed in all age groups, it is most common in children ages 1–3 years, with predilection for the bone (Society, 1987). Other common sites include the skin and lymph nodes. Disease presentation may be single organ or disseminated. When involvement is multisystemic, oral and gastrointestinal mucosa are often affected in addition to the spleen and liver, which are termed high-risk organs. Central nervous system symptomatology is usually secondary to bony involvement and may present as diabetes insipidus or spinal cord compression (Broadbent et al., 1994). Lung as a single organ involvement is usually restricted to adults, occurs almost exclusively in smokers, and may therefore be a separate, reactive disorder (Yousem, 2001).

Pure LHC of the female genital tract is rare, with only 32 reported cases after a worldwide literature search on Pubmed and Medline restricted to the English language (Table 1). We excluded any reports that included evidence of systemic disease. Age of presentation, location, treatment, remission status, and outcome were recorded.

The diagnosis is only confirmed via a biopsy with hematoxylin and eosin staining in addition to specific immunohistochemical staining. On hematoxylin and eosin, the biopsy classically consists of reniform Langerhans cells associated with an eosinophilic-rich inflammatory infiltrate. Pathological evaluation is confirmed by either positive staining for CD1a or CD207 (Langerin) markers. Generally, S-100 marker is also performed and is immunoreactive. Both CD1a and Langerin are transmembrane proteins expressed on Langerhans cell histiocytosis lesions and in normal Langerhans cells (Badalian-Very et al., 2013). Electron microscopy depicting Birbeck granules within the cellular cytoplasm is no longer required for the diagnosis of LHC (Cancer, 2008).

After the diagnosis of LCH of the female genital tract is made, it is important to perform a metastatic workup as a cutaneous lesion could be the first sign of multisystem involvement. Imaging scans of the head, chest, abdomen and pelvis as well as a bone marrow biopsy should be used to rule out hematogenous and other organ involvement. Case 2 was lost to follow up and thus was not able to have systemic work up performed.

Treatment of LCH vary substantially and there is not a standard of care for patients with pure genital involvement (Table 1). Treatment options for vulvar involvement include topical steroids, oral steroids,

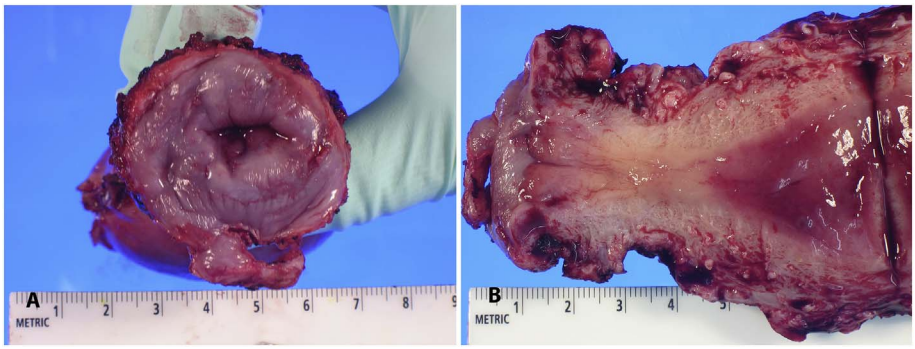

Fig. 3. (a) Gross specimen of cervix and uterus with view of multiparous cervical os. The cervix is shortened from prior LEEP procedure and almost flush with the vagina, but has a normal appearing ectocervix and an absent transformation zone. Some small endocervical nodularity can be seen at the os at 11–12 O'clock. (b) Gross specimen of bisected cervix and uterus, close-up of bisected cervix depicting lesion at os.

Table 1
"Pure" Genital Langerhans Cell Histiocytosis. PV: partial vulvectomy; RV: radical vulvectomy; RAD: radiation; Thal: Thalidomide; MTX: Methotrexate; Pred: Prednisone; INF: Interferon; Vinb: Vinblastine; Vinc: Vincristine; UR: unresponsive; NS: not specified; CR: complete remission; NED: no evidence of disease. Treatment was listed in order given to the patient.

Authors	Year	Age (years)	Affected site	Treatment	Response	Outcome (months)
Kierland[a]	1957	2	Vulva	Rad	CR	NED, 36 months
Rose[b]	1984	50	Vulva	Rad	CR	NS
Axiotis[c]	1990	85	Vulva	Topical Steroids	UR	NS
Voelklein[d]	1993	36	Vulva	Rad	CR	NS
Meehan and Smoller[e]	1998	76	Vulva	NS	NS	NS, 33 months
		54	Vulva	NS	NS	NS, 33 months
Solano[f]	2000	40	Vulva	Vinc, PV	UR- Chemo PV: CR	NED, 18 months
Pather[g]	2001	45	Vulva	Rad	CR	NED, 24 months
Rizvi[h]	2002	41	Vulva	Vulvectomy	CR	NED, 6 weeks
Santillan[i]	2003	33	Vulva	Rad, PV, RV, Thal	Rad/PV/RV-PR Thal-CR	NED, 12 months
Singh[j]	2003	32	Vulva	Rad, PV, RV, Thal,	Rad/PV/RV-PR Thalidomide- CR	NS
Padula[k]	2004	31	Vulva	PV, Rad, RV, Thal	PV/Rad/RV-PR Thalidomide-CR	NED, 19 months
Ishigaki[l]	2004	65	Vulva, perineum	Complete excision	CR	NED, 12 months
Dietrich[m]	2004	29	Vulva	Rad, oral steroids, topical steroids, PV, RV	PR	NS
Venizelos[n]	2006	64	Vulva	Rad, PV	CR	NED, 22 months
Mlyncek[o]	2006	63	Vulva	Topical steroids, RV and bilateral inguinal lymphadenectomy	CR	NED, 12 months
Mottl[p]	2007	16.5	Vulva	Topical steroids, Vinb and oral steroids, Chemo (2-chlorodeoxyadenosine)	Others: PR 2-CdA: CR	NED, 6 months
Elas[q]	2007	76	Vulva	Topical steroids, IV Vinc and Vinb	Chemo: CR	NED, 9 months
Beneder[r]	2008	49	Vulva	Rad, PV	CR	NED, 51 months
Pan[s]	2009	49	Vulva	Rad	CR	NED, 5 months
Hwang[t]	2009	1	Vulva	Topical steroids	CR	NED, 3 months
Triantafyllidou[u]	2009	52	Vulva	Topical steroids, PV	PV: CR	NED, 10 months
Simons[v]	2010	33	Vulva	Topical steroids, immunosuppressant (Tacrolimus) Rad, CO2 laser	NS	NS
Foley[w]	2011	62	Vulva	Topical steroids	CR	NED, 13 months
Jiang[x]	2012	46	Vulva	Topical steroids, PV, Vinb, Pred	Topical steroids: UR PV/chemo/Pred: CR	NED, 40 months
		40	Vulva	PV, Vinb and Pred	CR	NED, 36 months
		23	Cervix	Thal, Vinb and Pred, hysterectomy	Thal/Vinb/Pred: PR Hysterectomy: CR	NED, 12 months
El-Safadi[y]	2012	59	Vulva	RV, MTX, Thal (lenalidomide)	RV/MTX: PR Thal: CR	NED, 31 months
Chang[z]	2013	68	Vulva	Topical steroids	CR	NED, 6 months
Kurt[aa]	2013	60	Vulva	NS	NS	NS
Khoummane[bb]	2014	47	Vulva	PV	NS	NS
Sun[cc]	2014	28	Vulva	INF, Pred, MTX	CR	NED, 18 months
Current report	2017	26	Vulva	Vulvar biopsy	CR	NED, 23 months
		67	Vulva	Topical steroids, Vulvar biopsy	CR	NED, 130 months
		31	Cervix	Hysterectomy	CR	NED, 54 months

[a] Kierland R.B., Epstein J.G., Weber W.E. (1957). Eosinophilic Granuloma of Skin and Mucous Membrane Association with Diabetes Insipidus. AMA Arch Derm. 75(1):45-54.
[b] Rose, P.G., Johnston, G.C. and O'Toole, R.V. (1984). Pure cutaneous histiocytosis X of the vulva. Obstetrics & Gynecology. 64(4): 587-590.
[c] Axiotis C.A., Merino M.J., Duray P.H. (1991). Langerhans cell histiocytosis of the female genital tract. Cancer. 67(6):1650-60.
[d] Voelklein K., Horny H.P., Marzusch K., Dietl J. (1993). Primary Langerhans cell histiocytosis of the vulva. Gynecol Obstet Invest. 36(3):189-90.
[e] Meehan S.A., Smoller B.R. (1998). Cutaneous Langerhans cell histiocytosis of the genitalia in the elderly: a report of three cases. J Cutan Pathol. 25(7):370-4.
[f] Solano T., España A., Sola J., López G. (2000). Langerhans' cell histiocytosis on the vulva. Gynecol Oncol. 8(2):251-4.
[g] Pather S., Moodley J.M., Bramdev A. (2001). Isolated Langerhans cell histiocytosis of the vulva: a case report. J Obstet Gynaecol Res. 27(3):111-5.
[h] Rizvi, R. M., Nasreen, C., & Jafri, N. (2002). Histiocytosis X of the vulva. J Pak Med Assoc, 52(9), 430.
[i] Santillan, A., Montero, A. J., Kavanagh, J. J., Liu, J., & Ramirez, P. T. (2003). Vulvar Langerhans cell histiocytosis: a case report and review of the literature. Gynecol. Oncol, 91(1), 241-246.
[j] Singh A., Prieto V.G., Czelusta A., McClain K.L., Duvic M. (2003). Adult Langerhans cell histiocytosis limited to the skin. Dermatology. 207(2):157-61.
[k] Padula A., Medeiros L.J., Silva E.G., Deavers M.T. (2004). Isolated vulvar Langerhans cell histiocytosis: report of two cases. Int J Gynecol Pathol. 23(3):278-83.
[l] Ishigaki H., Hatta N., Yamada M., Orito H., Takehara K. (2004). Localised vulva Langerhans cell histiocytosis. Eur J Dermatol. 14(6):412-4.
[m] Dietrich, J. E., Edwards, C., Laucirica, R., & Kaufman, R. H. (2004). Langerhans cell histiocytosis of the vulva: two case reports. J Low Genit Tract Dis, 8(2), 147-149.
[n] Venizelos, I. D., Mandala, E., Tatsiou, Z. A., Acholos, V., & Goutzioulis, M. (2006). Primary langerhans cell histiocytosis of the vulva. Int J Gynecol Pathol, 25(1), 48-51
[o] Mlyncek, M., Uharcek, P., & Durcansky, D. (2006). Vulvar Langerhans' cell histiocytosis: a case report. Acta Obstet Gynecol Scand, 85(6), 753-755.
[p] Mottl H., Rob L., Stary J., Kodet R., Drahokoupilova E. (2007). Langerhans cell histiocytosis of vulva in adolescent. Int J Gynecol Cancer. 17(2):520-4.
[q] Elas, D., Benda, J. A., & Galask, R. P. (2008). Langerhans' cell histiocytosis of the vulva: the Iowa experience. J Reprod Med, 53(6), 417-419.
[r] Beneder C., Kuhn A., ImObersteg J., et al. (2008). Isolated Langerhans cell histiocytosis of the vulva: a case report and review of the literature. Gynecol Surg. 5:165-8.
[s] Pan Z., Sharma S., Sharma P. (2009). Primary langerhans cell histiocytosis of the vulva: report of a case and brief review of the literature. Indian J Pathol Microbiol. 52(1):65-8.
[t] Hwang C., Kim Y.J., Seo Y.J., Park J.K., Lee J.H., Lee Y. (2009). Isolated Langerhans cell histiocytosis of the vulva in an infant. Pediatr Dermatol. 26(6):751-3
[u] Triantafyllidou, O., Giannakopoulos, K., Pergialiotis, V., Simou, M., Lagkadas, A., & Alexandrou, P. (2009). Pure vulvar Langerhans cell histiocytosis: a case report and literature review. Eur J Gynaecol Oncol, 30(6), 691-694.
[v] Simons M., Van De Nieuwenhof H.P., Van Der Avoort I.A., Bulten J., De Hullu J.A. (2010). A patient with lichen sclerosus, Langerhans cell histiocytosis, and invasive squamous cell carcinoma of the vulva. Am J Obstet Gynecol. 203(2):e7-10.
[w] Foley, S., Panting, K., Bell, H., Leonard, N., & Franks, A. (2011). Rapid resolution of primary vulval adult Langerhans cell histiocytosis with very potent topical corticosteroids. Australas J Dermatol, 52(1), e8-e14.
[x] Jiang W., Li L., He Y.M., Yang K.X. (2012). Langerhans cell histiocytosis of the female genital tract: a literature review with additional three case studies in China Arch Gynecol Obstet., 285:99-103.
[y] El-Safadi S., Dreyer T., Oehmke F., Muenstedt K. (2012). Management of adult primary vulvar Langerhans cell histiocytosis: review of the literature and a case history. Eur J Obstet

Gynecol Reprod Biol. 163(2):123-8.
[z] Chang J.C., Blake D.G., Leung B.V., Plaza J.A. (2013). Langerhans cell histiocytosis associated with lichen sclerosus of the vulva: case report and review of the literature. J Cutan Pathol. 40(2):279-83.
[aa] Kurt, S., Canda, M. T., Kopuz, A., Solakoglu Kahraman, D., & Tasyurt, A. (2013). Diagnosis of primary langerhans cell histiocytosis of the vulva in a postmenopausal woman. Case Rep Obstet Gynecol, 2013, 962670.
[bb] Khoummane N., Guimeya C., Lipombi D., Gielen F. Vulvar Langerhans cell histiocytosis: a case report. Pan Afr Med J. 18:119 (2014).
[cc] Sun N., Cao D., Zhao Q., Li W. (2014). Langerhans Cell Histiocytosis on the Vulva: A Case Report and Review of the Literature. Journal of Reproduction & Contraception. 25(2): 123-128.

chemotherapy (vinblastine, vincristine, or 2-chlorodeoxyadenosine), immune modulators (methotrexate or tacrolimus), radiation, partial vulvectomy, radical vulvectomy with or without lymph node resection, thalidomide, and radiation therapy. Treatment options for cervical involvement have also included hysterectomy. Although there has been no consensus on the best treatment option, El-Safadi et al. (El-Safadi et al., 2012) argues that thalidomide should be considered as first-line treatment or as maintenance therapy due to his analysis demonstrating long lasting remission and minimal side effects. For cases 1 and 2, there were no residual lesions following vulvar biopsy. The biopsies had negative margins and no additional surgery or adjuvant treatment was deemed necessary. Similarly, in Case 3, the tumor was small with minimal invasion, and a simple hysterectomy was deemed adequate for local tumor control. Surgical margins were widely negative and thus no adjuvant radiation or chemotherapy was recommended for Case 3.

The initial post-treatment surveillance is interval history and physical 2–4 times per year and follow-up Pap smears annually for long-term surveillance for recurrence in the case of cervical involvement as recommended by the NCCN (ACOG, 2013). Patients with localized LCH, similar to our three patients, may experience spontaneous remission and a favorable outcome. Poor prognostic factors include spread outside the female genital tract to bone, liver and central nervous system. Therefore, during surveillance and follow-up it is prudent to place particular attention on these organ systems despite LCH presenting as a pure genital lesion (Jiang et al., 2012). In summary, we add to the literature three additional cases of female genital LCH. Similar to previously reported cases, prognosis for these lesions confined to the gynecologic tract appears to be favorable.

Conflicts of interest

All authors report no conflicts of interest.

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Competing interests

The authors declare that they have no competing interests related to this case report.

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References

ACOG, 2013. American College of Obstetricians and Gynecologists Bulletin.
Axiotis, C.A., Merino, M.J., Duray, P.H., 1991. Langerhans cell histiocytosis of the female genital tract. Cancer 67 (6), 1650–1660.
Badalian-Very, G., Vergilio, J.A., Fleming, M., Rollins, B.J., 2013. Pathogenesis of Langerhans cell histiocytosis. Annu. Rev. Pathol. 24 (8), 1–20.
Broadbent, V., Egeler, R.M., Nesbit Jr., M.E., 1994. Langerhans cell histiocytosis-clinical and epidemiological aspects. Br. J. Cancer Suppl. 23, S11–S16.
Cancer, I.A., 2008. WHO Classification of Tumours of Haematopoietic and Lymphod Tissue.
El-Safadi, S., Dreyer, T., Oehmke, F., Muenstedt, K., 2012. Management of adult primary vulvar Langerhans cell histiocytosis: review of the literature and a case history. Eur. J. Obstet. Gynecol. Reprod. Biol. 163 (2), 123–128.
Jiang, W., Li, L., He, Y.M., Yang, K.X., 2012. Langerhans cell histiocytosis of the female genital tract: a literature review with additional three case studies in China. Arch. Gynecol. Obstet. 285, 99–103.
Lichtenstein, L., 1953. Histiocytosis X: integration of eosinophilic granuloma of bone, Letterer Siwe disease, and Schuller-Christian disease as related manifestations of a single nosologic entity. Arch. Pathol. 56, 84–102.
Society, W.G., 1987. Histiocytosis syndromes in children. Lancet I (8526), 208–209.
Yousem, S., 2001. Pulmonary Langerhans' cell histiocytosis: molecular analysis of clonality. Am. J. Surg. Pathol. 630–636.