Vulvar Langerhans cell histiocytosis: Clinicopathologic characteristics, mutational profile, and treatment of 4 patients in a single-center cohort

Ruben Renier, MD,[a] Petra De Haes, MD, PhD,[b] Francesca Bosisio, MD, PhD,[b] Isabelle Vanden Bempt, PD, PhD,[c] and F. J. Sherida H. Woei-A-Jin, PhD, MD[d]

Key words: BRAF; gene mutation; Langerhans cell histiocytosis; skin; treatment; vulva.

INTRODUCTION

Previously regarded as reactive, Langerhans cell histiocytosis (LCH) is now recognized as an inflammatory myeloid neoplasm characterized by CD1a, CD207 (Langerin) and S100 expression, cytoplasmic Birbeck granules, and recurrent somatic activating mutations in the mitogen-activated protein kinase (MAPK) pathway.[1,2] The clinical spectrum ranges from a single lesion to disseminated multisystem (MS) involvement. Cutaneous LCH (30%) presents as often pruritic erythematous/skin-colored papules/pustules, or petechial/purpuric rash with variable scaling and crusting located on the scalp or intertriginous areas (mimicking seborrheic dermatitis and intertrigo). Mucosal LCH presents as ulcers (oral/genital) or itchy erythematous nodulopapular eruption (genital) (Fig 1, *A*). The patient consent form was obtained with permission to use Fig 1.

Vulvar Langerhans cell histiocytosis (vLCH) is rare, occurs at any age, and often heralds MS-LCH.[3,4] Topical skin treatment encompasses medium-high potency corticosteroids, nitrogen mustard, or imiquimod. For more extensive and/or therapy-resistant lesions, phototherapy or systemic therapy can be considered (methotrexate 20 mg 4 times a week, thalidomide 100-200 mg/d, hydroxyurea 1000 mg/d, chemotherapy).[4-7] When considering radiotherapy and surgery (eg, vulvectomy), the high relapse rate (62%) should be taken into account.[8] Drugs targeting the MAPK pathway are promising, but the mutational landscape in vLCH is mostly undocumented (*BRAF*^{V600E} reported once).[2,9]

Abbreviations used:

LCH:	Langerhans cell histiocytosis
MAPK:	mitogen-activated protein kinase
MS:	multisystem
vLCH:	vulvar LCH

CASE SERIES

From June 1, 1990, to January 1, 2022, 5 patients with vLCH were diagnosed at our center (Table I). Skin biopsies were retrieved for histopathologic confirmation in 4 patients (Fig 1, *B* and *C*) with routine mutational profiling in 3 of 4 specimens (1 was precluded due to tissue exhaustion). Genital symptoms developed at the ages 37-51 and led to the subsequent diagnosis of MS-LCH in 3 out of 4 patients, and 1 patient remained single system. Two patients were diagnosed years before with idiopathic diabetes insipidus, retrospectively a manifestation of LCH. Mutational profiling (next generation sequencing; Illumina platform) showed *BRAF* mutations in 3 patients: p. V600E (n = 1) and p. N486_P490del (n = 2). No mutations were found in

From the KU Leuven, Department of Dermatology, Leuven, Belgium[a]; KU Leuven, Department of Pathology, Leuven, Belgium[b]; KU Leuven, Department of Human Genetics, Leuven, Belgium[c]; and KU Leuven, University Hospitals Leuven, Department of General Medical Oncology, Leuven, Belgium.[d]

Funding sources: None.

IRB approval status: This study does not encompass any research with human subjects or animals, and was approved by the Ethics Committee of the University Hospitals Leuven (S64542).

Correspondence to: Ruben Renier, MD, Herestraat 49, UZ. 3000 Leuven, Belgium. E-mail: ruben.renier@uzleuven.be.

JAAD Case Reports 2023;36:78-81.

2352-5126

https://doi.org/10.1016/j.jdcr.2023.03.024

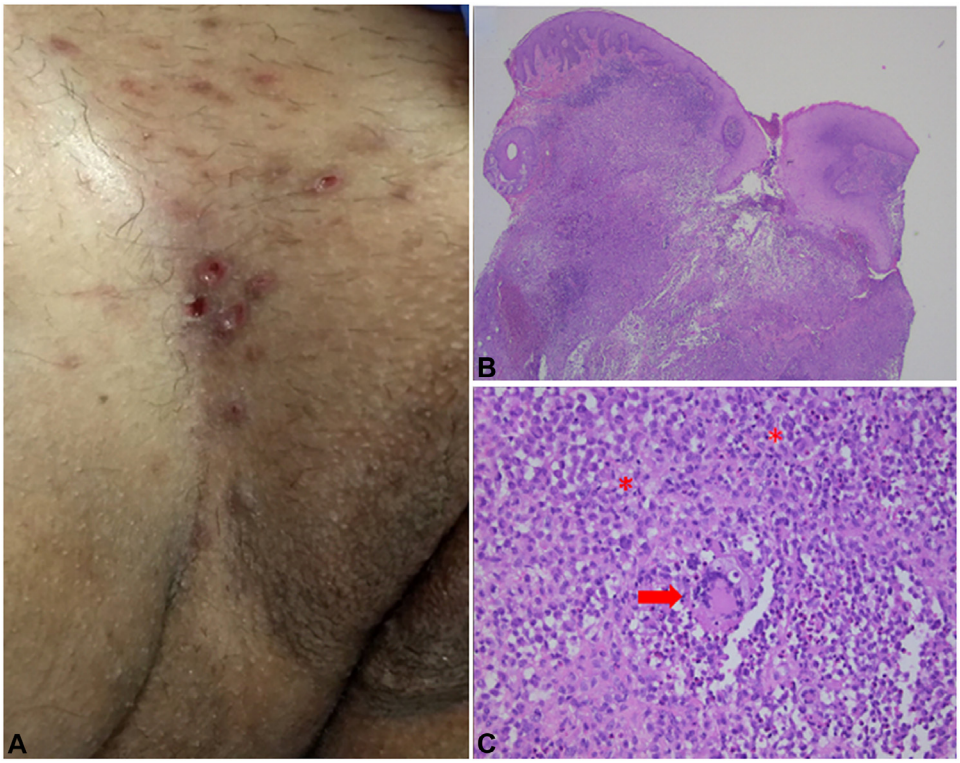

Fig 1. Representative clinical and histological image of vulvar Langerhans cell histiocytosis. **A**, Multiple punched out-ulcers in the right inguinal fold of patient 3. **B**, Accordingly, the skin biopsy showed central erosion surrounded by reactive epidermal hyperplasia, fibrinous deposition, and subcutaneous edema (Hematoxylin-eosin stain; original magnification: ×5). **C**, The inflammatory infiltrate was mixed and composed mainly by monocytes with large, bean-shaped nuclei (red asterisks), surrounded by numerous eosinophils and lymphocytes. Multinucleated giant cells were present (red arrow) (Hematoxylin-eosin stain; original magnification: ×10).

the MAPK and PI3K-pathway genes *KRAS, ARAF, MAP2K1, PIK3CA*, *PTEN*, *AKT1*, and *mTOR*. All 3 patients treated with potent topical corticosteroids obtained symptom alleviation and good (temporary) disease control. Two patients with MS-LCH refused first-line chemotherapeutic treatment. One chemotherapy-treated MS-LCH patient achieved a durable complete remission of all lesions except skin, which relapsed <6 months after treatment cessation. Hydroxyurea 500 mg twice a day was initiated and resulted in a good response. One MS-LCH *BRAF* p. N486_P490del patient consented to targeted therapy with BRAF-inhibitor dabrafinib 100 mg twice a day, resulting in rapid resolution of skin lesions and vulvar pain. However, due to side effects (ie, fever, arthralgia), treatment was switched to MEK-inhibitor trametinib 1 mg. The patient has remained in remission since.

DISCUSSION

Our case series illustrates that vLCH, often missed, may be the first sign of MS-LCH and stresses the importance to biopsy recurrent and chronic vulvar lesions. Biopsy additionally enables molecular profiling allowing the detection of clinically relevant MAPK pathway gene mutations such as *BRAF* p. N486_P490del, which is missed by digital droplet $BRAF^{V600E}$ PCR and targeted exon 15 sequencing. Both dabrafenib and trametinib proved active, although dabrafenib's long-term efficacy could not be assessed due to adverse events. As vLCH frequently relapses, a multidisciplinary approach remains essential and topical corticosteroids should always be considered for its favorable safety profile, adequate disease control, and alleviation of itching regardless of systemic treatment.

Table I. Clinicopathologic features, mutational profile, and treatment outcome of 4 patients with vulvar Langerhans cell histiocytosis

	Patient 1	Patient 2	Patient 3	Patient 4
Age at presentation	38 y	44 y	37 y	51 y
Cutaneous symptoms	Vulvar pruritus and small bumps.	Vulvar pruritus and superficial painful wounds.	Vulvar pruritus, ulcers Wounds in armpits and abdominal body folds.	Vulvar pain and ulcers, painful urination, fleeting red spots on arms and armpits.
Cutaneous signs	On left labium minor one slightly shiny lesion.	Erosions on labia minora. Erythematous plaques peri-vulvar, inguinal, perineal and on upper legs.	Generalized erythema of labia minora with induration. Punched out ulcers in right inguinal fold. Solitary eroded red papule on right breast.	Multiple red and grey small infiltrated papules on left arm, left leg and right labium major.
Histopathology	Hyperkeratosis and some acanthosis in epidermis. Underlying dermis shows dilated vessels with plump fibroblasts. Deeper cuts show bean-shaped cells with grooves, surroundded by eosinophils.	Irregular hyperplasia with parakeratosis of epidermis. Superficial dermis: round cells with eccentric bean-shaped nucleus, eosinophilic cytoplasm. Perivascular lymphocyte infiltrates, some eosinophils, granulocytes, melanophages.	Ulcerated epidermis with irregular acanthosis. Diffuse infiltration of dermis with oval cells with bean-shaped nucleus & eosinophilic cytoplasm. Background inflammation with numerous eosinophils, some granulocytes and lymphocytes.	Erosive acanthotic epidermis, with parakeratosis, spongiosis and neutrophil infiltrate. Dermis: dense and diffuse infiltrate with neutrophils, lymphocytes, plasma cells, some histiocytes with bean-shaped nucleus, and eosinophils.
Immunohistochemical staining	$CD1a^+$ $CD207^+$ $S100^+$	CD1 inconclusive CD207: no tissue left $S100^+$	$CD1a^+$ $CD207^+$ $S100^+$	$CD1a^+$ $CD207^+$ $S100^+$
BRAF mutation status	*BRAF* p.V600E	Wildtype exon 11, 15	*BRAF* p.N486_P490del	*BRAF* p.N486_P490del
Other clinical findings	Absent	Absent	Hypothyroidism, diabetes insipidus (5y), growth hormone deficiency, persistent ear infections (2 y).	Panhypopituitarism, diabetes insipidus (9y), recurrent ear infection, vertigo, fatigue.
Classification	Multisystem (skin, orbital bone, lung, intestinal)	Single system unifocal (after 5.5-y follow-up: pituitary gland)	Multisystem (skin, thyroid, pituitary gland, ear canals)	Multisystem (thyroid, pituitary gland, skin, ear canal, joints, intestine)
Systemic treatment	Refused	Not indicated.	Chemotherapy*	Refused chemotherapy Dabrafenib/trametinib
Topical treatment: *initial effect on lesions*	Potent to ultra-potent corticoids: *resolution of lesions and itch.*	Potent to ultra-potent corticoids: *resolution of lesions and itch.*	Potent corticoids: *partial response, good effect on itchiness.*	Not attempted
Cutaneous relapse	Recurrent vulvar lesions, disease control with topical corticoids.	Recurrent vulvar lesions, disease control with topical corticoids.	Remission during systemic therapy. Relapse $<$ 6 mo after end of treatment.	Complete remission with ongoing systemic therapy (follow-up: 10 mo).

In patient 1, two recurrent lesions were excised with good results albeit new vulvar lesions appeared. In patient 2, tissue exhaustion precluded mutation analysis of ARAF, AKT1 and mTOR. In addition, resequencing was not possible and the presence of a BRAF exon 12 deletion could not be excluded. Patient 3, in addition to BRAF p.Asn486_Pro490del, demonstrated variants of unknown significance in DNA repair gene POLE p.Ala1288_Leu1295del and tumor suppressor gene BRCA1 p.Val740Leu. In patient 4, karyotyping of LCH cells showed populations with extra chromosomes: 48,XX,+5,+7 and 46-47,XX,nca.

*Chemotherapy consisted of induction with vinblastine-prednisolone followed by consolidation with 6-mercaptopurine, vinblastine and prednisolone.

Conflicts of interest

The authors declare no competing interests.

REFERENCES

1. Facchetti F, Berti E. Langerhans cell histiocytosis. In: Elder DE, Massi D, Scolyer RA, Willemze R, eds. *WHO Classification of Skin Tumours*. 4th ed; 2018:281-282.
2. Rodriguez-Galindo C, Allen CE. Langerhans cell histiocytosis. *Blood*. 2020;135(16):1319-1331. https://doi.org/10.1182/blood.2019000934
3. Zudaire T, Guarch R, Valcayo A, et al. Primary Langerhans cell histiocytosis of the vulva: case report and review of the literature. *Int J Gynecol Pathol*. 2017;36(2):111-114. https://doi.org/10.1097/PGP.0000000000000303
4. Wieland R, Flanagan J, Everett E, Mount S. Langerhans cell histiocytosis limited to the female genital tract: a review of literature with three additional cases. *Gynecol Oncol Rep*. 2017;22:4-8. https://doi.org/10.1016/j.gore.2017.08.005
5. Steen AE, Steen KH, Bauer R, Bieber T. Successful treatment of cutaneous Langerhans cell histiocytosis with low-dose methotrexate. *Br J Dermatol*. 2001;145(1):137-140. https://doi.org/10.1046/j.1365-2133.2001.04298.x
6. Sander CS, Kaatz M, Elsner P. Successful treatment of cutaneous langerhans cell histiocytosis with thalidomide. *Dermatology*. 2004;208(2):149-152. https://doi.org/10.1159/000076491
7. Zinn DJ, Grimes AB, Lin H, Eckstein O, Allen CE, McClain KL. Hydroxyurea: a new old therapy for Langerhans cell histiocytosis. *Blood*. 2016;128(20):2462-2465. https://doi.org/10.1182/blood-2016-06-721993
8. El-Safadi S, Dreyer T, Oehmke F, Muenstedt K. Management of adult primary vulvar Langerhans cell histiocytosis: review of the literature and a case history. *Eur J Obstet Gynecol Reprod Biol*. 2012;163(2):123-128. https://doi.org/10.1016/j.ejogrb.2012.03.010
9. Gordon MS, Gordon MB. Occult Langerhans cell histiocytosis presenting with papillary thyroid carcinoma, a thickened pituitary stalk and diabetes insipidus. *Case Rep Endocrinol*. 2016;2016:5191903. https://doi.org/10.1155/2016/5191903