Case Report

Vulvar and Perineal Langerhans Cell Histiocytosis with BRAF V600E Mutation, Present in a Background of Condyloma Acuminatum

Tina Wong, DO; Nusrat Hussain, MD; Frank Chen, MD, PhD, MBA*

Department of Pathology and Anatomical Sciences, University at Buffalo, Buffalo, NY

Langerhans cell histiocytosis (LCH), previously known as Histiocytosis X, is a rare disorder characterized by clonal proliferation of bone marrow-derived, antigen-presenting Langerhans cells. Involvement of the lower female genital tract is quite unusual. Here we report a case of vulvar and perineal LCH with BRAF V600E mutation, present in a background of condyloma acuminatum. A 59-year-old woman with history of high grade squamous intraepithelial lesion (HSIL) presented with vulvar lesions. She underwent surgery involving cervix, vulva and perineal skin nodules. Grossly, the vulvar and perineal skin showed hair-bearing skin with partially crusted, vaguely nodular skin lesions. Microscopically, it showed a diffuse cellular infiltrate within the dermis with abundant pale cytoplasm, nuclear grooves and folds, fine nuclear chromatin and indistinct nucleoli. The differential diagnoses including LCH, Rosai-Dorfman disease and Erdheim-Chester disease. Condyloma acuminatum is present in the background. By Immunohistochemical studies (IHCs), the cells were positive for S100, CD1a and CD4 and were negative for pancytokeratin, CK7, CAM5.2, HMB45 and MART-1. SOX-10 showed cytoplasmic and high background staining. Toludine blue was negative. In summary, morphologic and IHCs profile was consistent with LCH. Further clinical history showed that this patient had been diagnosed with stage IV systemic LCH with multiple bone lesions. She showed BRAF V600E mutation and had been treated with oral Vemurafenib. In conclusion, LCH involving vulva and perineal skin, either isolated or as part of systemic disorder, is very rare. A careful histopathologic examination and immunohistochemical studies are necessary to confirm such a diagnosis.
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Key Words: *Langerhans Cell Histiocytosis; BRAF V600E mutation; Condyloma Acuminatum; Vulvar lesions*

INTRODUCTION

Langerhans cells, first described by Paul Langerhans in 1868, play a critical role in our immune system. Langerhans cell histiocytosis (LCH) is a rare neoplastic disorder and was previously known as Histiocytosis X. It is characterized by monoclonal proliferation of Langerhans cells, initially in the bone marrow and later, presenting as a single organ or a systemic disorder involving various organs such as skin, bone marrow, spleen, lung, liver and central nervous system. LCH of the female genital tract is rare and may involve vulva, vagina, cervix, endometrium, and ovary.

CASE PRESENTATION

We describe a 59-year-old woman who presented with vulvar lesions, suggestive of condyloma acuminata. Multiple biopsies from vulva, groin and perineal skin were submitted for histological examination. Besides condylomas, vulvar and perineal LCH was diagnosed. Further patient work up showed bone lesions in the femur involving bone marrow. Brain MRI was negative for tumor involvement. She was staged as vulva LCH stage 4 and started on treatment.

RESULTS

Upon macroscopic examination of the vulva and perineal skin specimen, slightly raised and vaguely nodular lesions were identified with no ulceration and/or pigmentation. Microscopic examination showed epidermal koilocytes, consistent with condyloma acuminatum (**Figures 1** and **2**). A diffuse and atypical mononuclear cell infiltrate involving the reticular dermis (**Figure 2**). The individual cells had abundant pale cytoplasm, eccentric nuclei with grooves, fine chromatin and indistinct nucleoli (**Figure 2**). By immunohistochemistry, the neoplastic cells were diffusely positive for S100 (**Figure 3**), CD1a (**Figure 4**) and CD4; and were negative for HMB45, Mart-1, pancytokeratin, CK7 and CAM5.2. Toulidine blue (a mast cell marker) was also negative. The overall histological features and immunoprofile were consistent with LCH involving vulva and perineal skin. Further investigations into her clinical history revealed that this patient had been diagnosed with systemic LCH with B-Raf proto-oncogene (BRAF) V600E/V600K somatic mutation.

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***Corresponding Author:** 115 Flint Road, Department of Pathology and Anatomic Sciences, University at Buffalo, Buffalo, NY 14221.
(Email: fchen@kaleidahealth.org)

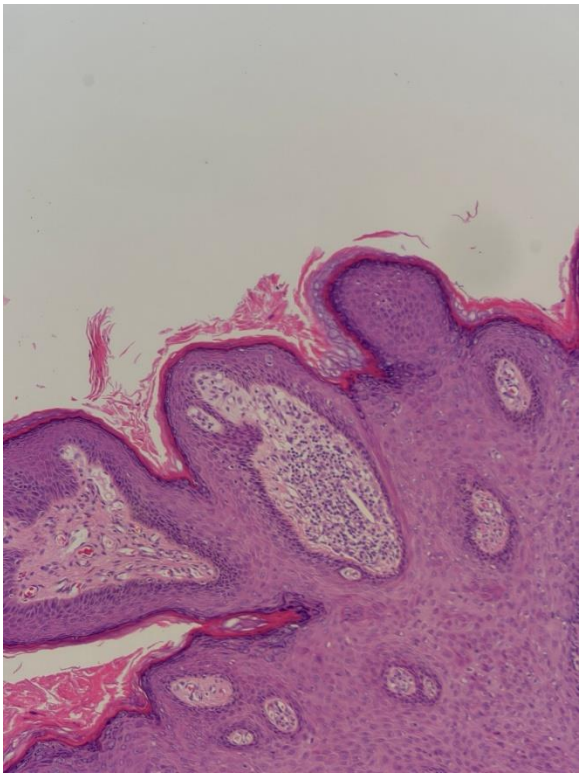

Figure 1. Low power view shows condyloma acuminatum with cellular infiltrate in the dermis. (H&E, 100x)

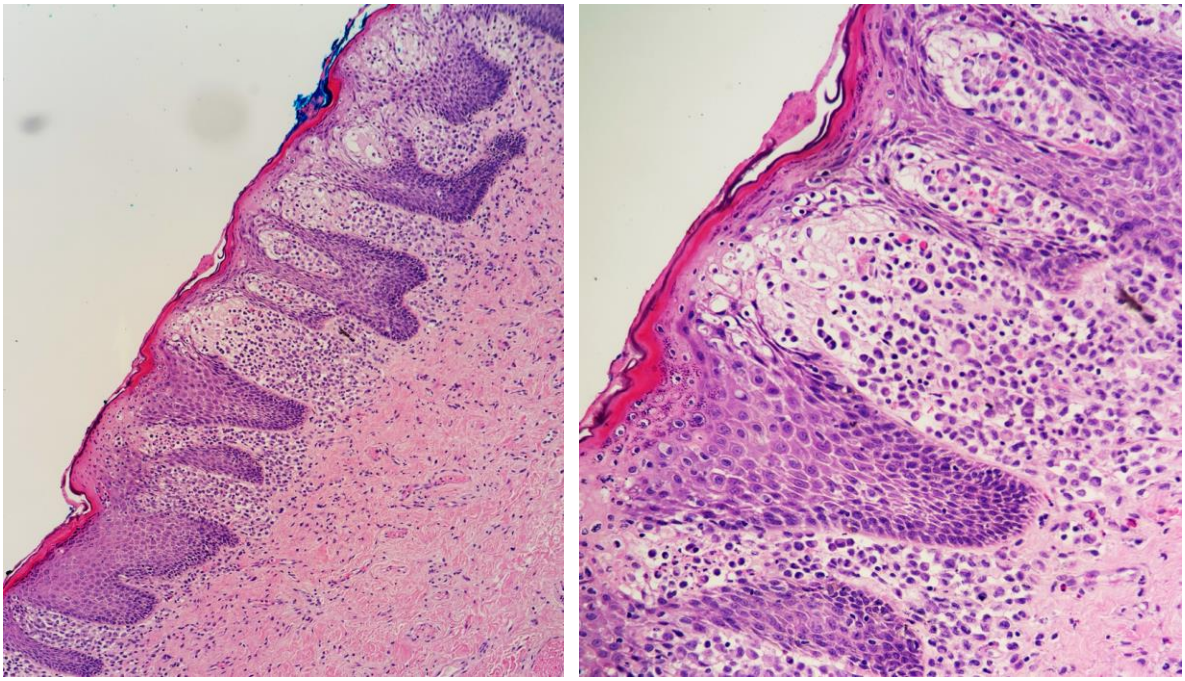

Figure 2. H&E shows diffuse cellular infiltrate in the dermis with abundant pale cytoplasm, nuclear grooves and folds, fine nuclear chromatin and indistinct nucleoli in 100x (1A) and 400x (1B).

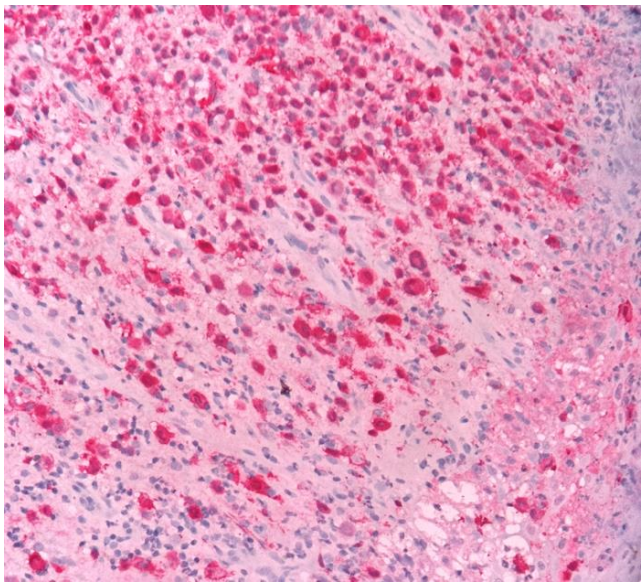

Figure 3. S100 with cytoplasmic and nuclear staining.

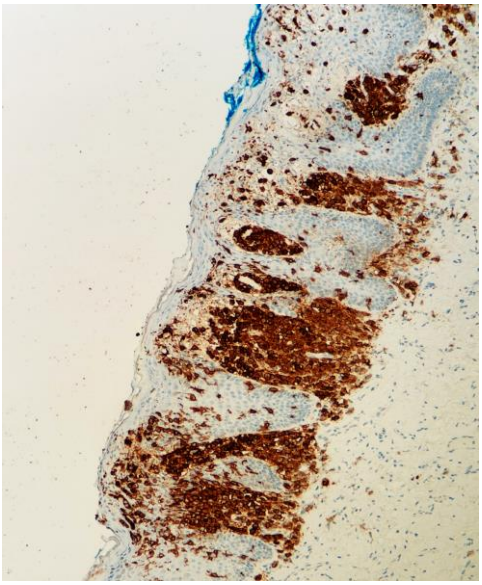

Figure 4. CD1a with membranous staining.

CONCLUSION

Condyloma acuminatum is a common sexually transmitted disease resulting in anogenital warts due to human papillomavirus (HPV). There is a high prevalence of condyloma acuminatum to occur in the vulva.[1] The wart-like lesions have variable appearances: white, pink, brown in color and flat, papillary or cerebriform in architecture. Histologic evaluation will show acanthosis with hyperkeratosis, papillomatosis and koilocytes.[2] Persistent HPV infection can lead to the development of cervical intraepithelial neoplasia, which could lead to invasive cervical cancer.

HPV can be transmitted by sexual, anal or genital contact. HPV strains can be divided into low-risk and high-risk. Low-risk types like HPV 6 and 11 are the most predominant strains in developing condyloma acuminatum. HPV 16 and 18 are high-risk types that could lead to premalignant entities, like low grade squamous intraepithelial lesion (LSIL) and high grade squamous intraepithelial lesion (HSIL).

Microscopically, LSIL has nuclear atypia in the including nuclear enlargement, irregular contours and hyperchromatic. Koilocytes are often present in LSIL, which includes raisinoid nuclei with a perinuclear halo in the superficial layers.[3] HSIL has full thickness nuclear atypia of coarse chromatin, irregular contour and prominent nucleoli with high nuclear to cytoplasmic ratio. The most common high-risk HPV subtype found in atypical squamous cells of undetermined significance (ASCUS) and LSIL is HPV 16, with monoinfection of HPV 16 identified in 41% of women with ASCUS and LSIL.[4] HSIL can progress from LSIL, and lesions that progress into higher grade tends to be HPV 16 positive.

Normal Langerhans cells are bone marrow-derived dendritic cells, which later populate the epidermis and characteristically express CD1a surface protein. Langerhans cell histiocytosis is a rare entity that is more often seen within the childhood and adolescent population.[5] LCH is a neoplastic proliferation of cells which share morphologic features and immunophenotype with normal Langerhans cells. The etiology of LCH is unknown and clinical spectrum varies from single-organ indolent disease to a fulminant and multisystem illness.6 Ulcerated or nodular vulvar lesion in women and perineal lesions in men have been described in association with multiorgan disease. Genital LCH has been classified into four distinct groups, based on initial clinical presentation and natural history of the disease; 1. “pure” genital LCH; 2. Genital LCH with multiorgan involvement; 3. Oral/cutaneous LCH with subsequent genital or multiorgan involvement and 4. Diabetes insipidus with subsequent genital or multiorgan involvement.[7] The prognosis is more favorable with an isolated case of LCH, compared to a multisystem disease.

The most frequent location in LCH of female genital tract is vulva but it can arise anywhere along the tract. Our patient presented with an abnormal Pap smear and presence of low-risk human papilloma virus (HPV). Her cervical HSIL was confirmed, however, vulvar and perineal skin lesions showed an atypical mononuclear cell infiltrate with characteristic nuclear morphology of grooved nuclei with eosinophilic cytoplasm. In the background, there were scattered eosinophils. The differential diagnoses included Rosai-Dorfman disease and Erdheim-Chester disease. The immunohistochemical stains, especially presence of CD1a, confirmed the diagnosis of genital LCH.

There are four types of histiocytic neoplasms including LCH, Rosai-Dorfman disease, Edheim-Chester disease and ALK-positive histiocytosis. Rosai-Dorfman disease presents with histiocytes with nuclear features of round to oval nuclei, prominent nucleoli, fine chromatin and pale cytoplasm with engulfment of inflammatory cells.[8] Immunohistochemistry stains would show expression of S100, cyclin D1 and OCT2.

The histiocytes are negative for CD1a and langerin. Erdheim-Chester disease presents with epithelioid or spindled histiocytes. Histiocytes from Erdheim-Chester disease will express S100, CD163 and factor XIIIa.[8] ALK-positive histiocytosis is a systemic entity that includes the liver and spleen in infants and a disease with central nervous system involvement in adults. ALK-positive histiocytosis has similar features to Rosai-Dorfman disease: histiocytes with engulfment of inflammatory cells with expression of OCT2 and S100.[8]

BRAF V600E mutation is significantly associated with LCH lesions, particularly in the pediatric population. It regulates cellular proliferation and plays a key role in oncogenesis by triggering mitogen-activated protein kinase signaling in most LCH patients.[9] The treatment options include topical skin treatment with high-strength corticosteroids, phototherapy, methotrexate and surgical excisions.

Vulvar LCH can be the first sign of systemic disease and can often be missed.[10] Therefore, recurrent and chronic vulvar lesions must be biopsied. Our patient presented with vulvar and perineal LCH, and was later found to have bone lesions in the femur involving the bone marrow. Patient had received LCH treatment and follow up is recommended.

CONFLICT OF INTEREST DISCLOSURES

The authors have no conflict of interest to disclose.

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