Case series

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

Rebekah Wieland\textsuperscript{a,b,\textdagger}, Jenna Flanagan\textsuperscript{b}, Elise Everett\textsuperscript{b}, Sharon Mount\textsuperscript{c}

\textsuperscript{a} College of Medicine, University of Vermont, Burlington, VT, USA
\textsuperscript{b} Gynecological Oncology, Department of Obstetrics, Gynecology and Reproductive Sciences, The University of Vermont Medical Center, Burlington, VT, USA
\textsuperscript{c} Department of Pathology and Laboratory Medicine, The University of Vermont Medical Center, Burlington, VT, USA

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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 Valacyclovir. HSV results returned negative and Valacyclovir 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...
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
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,
Table 1

| Authors                          | Year  | Age (years) | Affected Site | Treatment                                      | Response | Outcome (months) |
|---------------------------------|-------|-------------|--------------|------------------------------------------------|----------|------------------|
| Kierland (2)                    | 1957  | 2           | Vulva        | Rad                                            | CR       | NED, 36 months   |
| Rose (2)                        | 1984  | 50          | Vulva        | Rad                                            | CR       | NS               |
| Axosis (3)                      | 1990  | 85          | Vulva        | Topical Steroids                               | UR       | NS               |
| Voelklein (3)                   | 1993  | 36          | Vulva        | Rad                                            | CR       | NS, 33 months    |
| Meehan and Smoller (4)          | 1998  | 76          | Vulva        | NS                                             | NS       | NS, 33 months    |
| Solano (5)                      | 2000  | 40          | Vulva        | Vinc, PV                                       | UR: Chemotherapy | NED, 18 months |
| Father (6)                      | 2001  | 45          | Vulva        | Rad                                            | CR       | NED, 24 months   |
| Rizvi (7)                       | 2002  | 41          | Vulva        | Vinc                                            | CR       | NED, 6 weeks     |
| Santillan (8)                   | 2003  | 33          | Vulva        | Rad, PV, Thal                                   | Thal:CR  | NED, 12 months   |
| Singh (9)                       | 2003  | 32          | Vulva        | Rad, PV, Thal                                   | Rad/Thal-CR | NS               |
| Padula (10)                     | 2004  | 31          | Vulva        | PV, Rad, Thal                                   | Thalidomide-CR | NED, 19 months |
| Ishigaki (11)                   | 2004  | 65          | Vulva, perineum | Complete excision                            | CR       | NED, 12 months   |
| Dietrich (12)                   | 2004  | 29          | Vulva        | Rad, oral steroids, topical steroids, PV, RV   | PR       | NS               |
| Venets (13)                     | 2006  | 64          | Vulva        | Rad, PV                                        | CR       | NED, 22 months   |
| Mlynec (14)                     | 2006  | 63          | Vulva        | Topical steroids, RV and bilateral inguinal lymphadenectomy | CR       | NED, 12 months   |
| Mottl (15)                      | 2007  | 16.5        | Vulva        | Topical steroids, Vinc and oral steroids, Chemo (2-chlorodeoxyadenosine) | Others:PR | NED, 6 months    |
| Elas (16)                       | 2007  | 76          | Vulva        | Topical steroids, IV Vinc and Vinc            | Chemotherapy: CR | NED, 9 months   |
| Benner (17)                     | 2008  | 49          | Vulva        | Rad, PV                                        | CR       | NED, 51 months   |
| Pan (18)                        | 2009  | 49          | Vulva        | Rad                                            | CR       | NED, 5 months    |
| Hwang (19)                      | 2009  | 1           | Vulva        | Topical steroids                               | CR       | NED, 3 months    |
| Triantafyllidou (20)            | 2009  | 52          | Vulva        | Topical steroids, PV                           | PV: CR   | NED, 10 months   |
| Simons (21)                     | 2010  | 33          | Vulva        | Topical steroids, immunosuppressant (Tacrolimus) Rad, CO2 laser | NS       | NS               |
| Foley (22)                      | 2011  | 62          | Vulva        | CR                                             | Topical steroids: UR | NED, 13 months |
| Jiang (23)                      | 2012  | 46          | Vulva        | Topical steroids, PV, Vinc, Pred              | Topical steroids: UR | NED, 40 months   |
| El-Safadi (24)                  | 2012  | 59          | Vulva        | PV, MTX, Thal (lentilidolide)                  | Thal:CR  | NED, 31 months   |
| Chang (25)                      | 2013  | 68          | Vulva        | Topical steroids                               | CR       | NED, 6 months    |
| Kurt (26)                       | 2013  | 60          | Vulva        | NS                                             | NS       | NS               |
| Khummane (27)                   | 2014  | 47          | Vulva        | PV                                             | NS       | NS               |
| Sun (28)                        | 2014  | 28          | Vulva        | INF, Pred, MTX                                 | CR       | NED, 18 months   |
| Current report                  | 2017  | 26          | Vulva        | VB: Topical steroids, Vinc: Topical steroids, Vulvar biopsy | CR       | NED, 23 months   |
|                                | 2017  | 67          | Vulva        | Topical steroids, Topical steroids, Vulvar biopsy | CR       | NED, 130 months  |
|                                | 2017  | 31          | Vulva        | Gervix Thal, Pred, hystereectomy               | Gervix Hysterection: CR | NED, 54 months   |

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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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