

Primary diffuse large B cell lymphoma of the vulva—Two new cases of a rare entity and review of the literature



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Key words: diffuse large B-cell lymphoma; primary cutaneous non-Hodgkin lymphoma; vulvar lymphoma.

INTRODUCTION

With fewer than two dozen detailed cases reported in the literature, primary diffuse large B-cell lymphoma (DLBCL) of the vulva is a rare entity.

Although non-Hodgkin lymphomas (NHL) such as DLBCL most often arise from lymph nodes, bone marrow, or spleen, up to 24% of NHL can present primarily at extranodal sites such as the gastrointestinal tract and skin.¹ Less common is the occurrence of primary extranodal NHL at sites along the female genital tract. Although disseminated lymphomas frequently involve structures within the female genital tract, only an estimated 1.5% of NHL are primary extranodal tumors of the female genital tract, anatomically reported in the following order of prevalence: ovary (49%), uterus (29%), fallopian tube (11%), vagina (7%), and vulva (4%).^{1,2} Of these sites, DLBCL is the most common subtype of primary NHL identified within the female genital tract in general and in the vulva specifically.³

We report 2 new cases of primary DLBCL of the vulva with associated literature review.

CASE REPORTS

Case 1

A 38-year-old HIV-negative woman from Iraq, gravida 2 para 2, presented with 1-week history of a vulvar ulceration, which yielded positive herpes simplex virus (HSV) 2 direct fluorescent-antibody, treated with valacyclovir. Over the next 8 months, slow enlargement of minimally tender nodular

Abbreviations used:

CHOP:	cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone
DLBCL:	diffuse large B-cell lymphoma
GCB:	germinal center B cell
HSV:	herpes simplex virus
NHL:	non-Hodgkin lymphoma

induration at the site prompted biopsy of an approximately 1- to 2-cm tumor.

Histopathology found dense sheets of large lymphoid cells staining positively for CD20, PAX-5, CD-79, Bcl-2, and MUM1, consistent with DLBCL, with features compatible with primary DLBCL, leg type (Fig 1).⁴ No constitutional symptoms or lymphadenopathy were reported.

Positron emission tomography/computed tomography scan and bone marrow biopsy found no evidence of systemic involvement, yielding Ann Arbor stage IE. She underwent definitive localized radiation therapy (total dose of 36 Gy in 18 fractions followed by an electron boost to the vulva of 6 Gy) with remission of her disease, with continued remission 7 years later.

Case 2

A 73-year-old woman of European descent, gravida 2 para 2, presented with a 2-month history of a mass involving the clitoris and right anterior aspect of the labium minus, measuring 4 × 2 × 1.5 cm. Initial biopsy found a dense lymphoid infiltrate composed

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Funding sources: None.

Conflicts of interest: None disclosed.

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JAAD Case Reports 2018;4:962-7.

2352-5126

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<https://doi.org/10.1016/j.jidcr.2018.06.023>

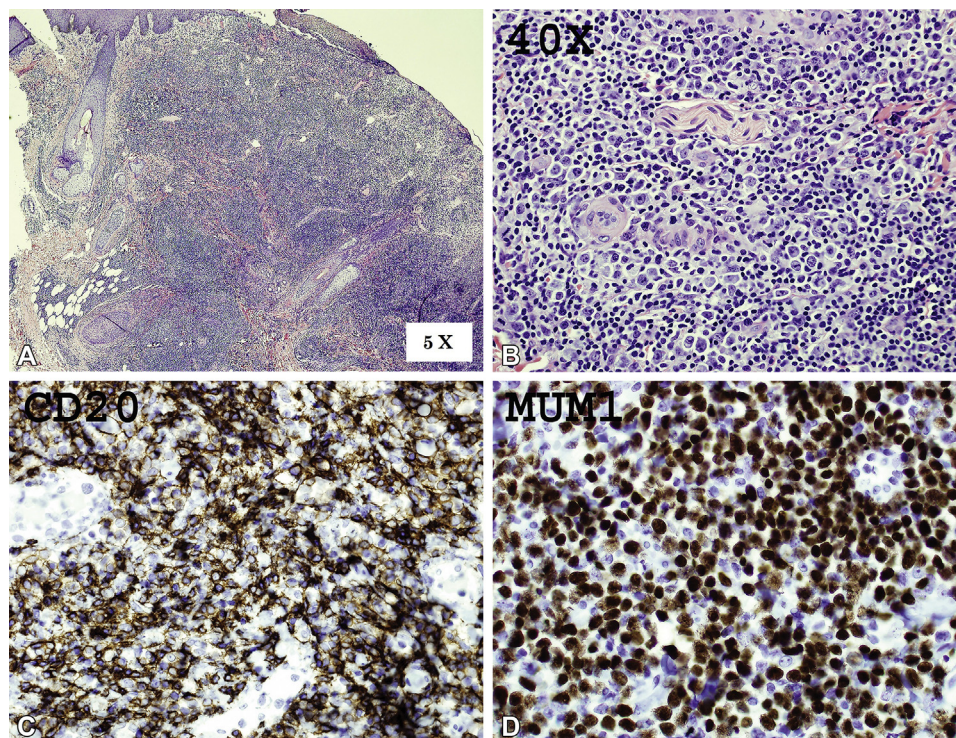


Fig 1. Histopathology findings of 38-year-old woman with enlarging vulvar nodule after treatment of HSV2. **A**, A diffuse lymphoid infiltrate (H&E stain; original magnification $\times 50$). **B**, Dense sheet of large atypical lymphocytes (H&E stain; original magnification $\times 400$). **C**, CD20⁺ stain. **D**, MUM1⁺ stain.

of CD20⁺ lymphocytes featuring medium- to large-sized centroblastlike cells, co-expressing Bcl-2, CD23, and weak CD10, but not Bcl-6, CD3, CD5, or cyclin D1. Wide excision of the lesion 3 weeks later found large cells in a vaguely nodular pattern (Fig 2) staining positively for CD20, CD10, Bcl-2, Bcl-6, and MIB-1 (60%) but negatively for MUM1 and Epstein-Barr encoding region, interpreted as DLBCL, germinal center B-cell (GCB) type.

Bone marrow biopsy and 18F-fluorodeoxyglucose positron emission tomography-computed tomography scan found no further evidence of malignancy, yielding Ann Arbor Stage IE. No further therapy was administered. No systemic disease has been seen by computed tomography imaging during surveillance up to 65 months from diagnosis.

DISCUSSION

These 2 cases add experience with primary vulvar DLBCL to our limited literature to date, thereby expanding our understanding of this poorly characterized condition. Our cases share the similar clinical presentation of a localized enlarging mass, with the first case notably preceded by herpetic infection. Pathologically, both cases manifested classic DLBCL architecture and cytomorphology;

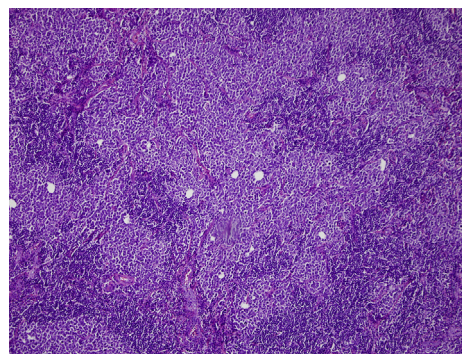


Fig 2. Vulvar tissue taken from 73-year-old woman with enlarging vulvar mass shows dense lymphoid cells in vague nodular pattern. (Hematoxylin-eosin stain; original magnification: $\times 100$.)

by immunohistochemistry, the first case exhibited a profile more in keeping with classic leg type primary cutaneous DLBCL (MUM-1 positive), whereas the second case qualified as a GCB-type DLBCL (CD10 and Bcl-6 positive). Both cases shared good response to local therapy.

Review of the literature on primary vulvar DLBCL is limited by small numbers and retrospective nature of reports, variably detailed immunohistochemical

Table I. Primary vulvar DLBCL cases with localized presentation (Ann Arbor stages I and II)

Patient number	Reference	Age	PMH	Clinical presentation	Size	Ann Arbor stage	Histopathology	Initial treatment	Outcomes
1	Ye et al, 2018, current report	38	G2P2, Iraqi	Valacyclovir-treated initial HSV ulceration preceded growth of underlying nodule	1-2 cm	IE	PCDLBCL-LT	RT	AWOD at 7 y
2	Ye et al, 2018, current report	73	G2P2, European descent	2-mo history of enlarging mass	4 × 2 × 1.5 cm	IE	DLBCL (GCB-type)	Local excision	AWOD at 65 mo
3	Clement et al, 2016 ⁵	43	Recurrent pseudolymphoma of inguinal region, nulliparous, tobacco user	6-mo history of nontender, movable mass	3.2 cm	IIE	DLBCL (GCB-type)	Local excision, followed by 6 cycles of R-CHOP with CR	Remission at 6 mo
4	El Kacemi et al, 2015 ⁶	37	Primiparous	Pruritic, painful, ulcerating mass	13 × 7 cm	IIE	DLBCL	4 cycles of R-CHOP, followed by RT with CR	AWOD at 36 mo
5	Plaza et al, 2011 ⁷	—	—	No evidence of extracutaneous disease	—	IE	PC-DLBCL (NOS)	—	—
6	Signorelli et al, 2007 ¹	75	—	—	—	IE	DLBCL	5 cycles of CHOP with CR	Recurrence at 10 mo. Given additional 4 cycles R-CHOP with CR. AWOD at 21 mo
7	Kosari et al, 2005 ⁸	>19	—	—	—	Localized — unknown staging	DLBCL	—	—
8	Tjalma et al, 2002 ⁹	73	TAH & unilateral SO for myomas, nulliparous, HIV negative	5-mo history of enlarging mass	3 × 1.5 cm	IE	DLBCL	Local excision, followed by RT with CR	Recurrence at 6 mo. Given additional 6 cycles CHOP with CR. AWOD at 51 mo
9	Vang et al, 2001 ³	67	—	Pruritic mass	—	IIE	DLBCL	CT and RT with CR	Recurrence in spine. DOD at 2 y
10	Vang et al, 2001 ³	71	—	Mass	—	IE	DLBCL	—	—
11	Vang et al, 2001 ³	68	—	Mass with ulceration 7 cm	7 cm	Unknown	DLBCL	—	—

12	Iczkowski et al, 2000 ¹⁰	64	White, G1P1, TAHBSO for leiomyomas & adenomyosis	Localized erythema and swelling with nontender induration and overlying ulceration; No evidence of extracutaneous disease	3 × 2 cm for left side; bilateral labial swelling	Localized — unknown staging	DLBCL	CHOP with CR	AWOD at 12 mo
13	Macleod et al, 1998 ¹¹	51	Multiparous, TAHBSO for benign tumor	2-y history of pruritic right anterior labium minus mass and underwent excision with local recurrence 6 mo later	2.6 × 1.2 × 0.8 cm	IE	DLBCL	Local excision and RT with CR	AWOD at 30 mo
14	Kaplan et al, 1996 ¹²	25	African American, HIV+, laser genital wart removal 8 mo prior	3-mo history of painful, edematous mass with overlying ulceration; 20lb weight loss over prior 6 mo	10 × 10 × 12 cm	IE	DLBCL	3 cycles modified low dose CHOP-bleomycin without significant response. Switched to RT with partial response	DOD at 7 mo
15	Marcos et al, 1992 ¹³	79	Multiparous	1-mo history of enlarging, nonpainful mass	6 × 4 cm	IE	DLBCL	RT with CR	AWOD at 10 mo
16	Nam et al, 1992 ¹⁴	68	Korean, multiparous	1-y history of movable, nontender mass	5 × 4.5 × 2.5 cm	IE	DLBCL	Local excision	AWOD at 14 mo
17	Bagella et al, 1990 ²	61	—	Mass with surrounding edema	—	IE	DLCL	Local excision, PROVECIP with CR	DWD at 10 mo due to unknown cause
18	Sneddon and Wishart, 1972 ¹⁵	42	7-y history of dermatomyositis and recently started on azathioprine	3-mo history of dyspareunia with vulvar ulceration and vaginal discharge	—	Unknown	DLCL (reticulum cell sarcoma)	RT	AWOD at 10 mo
19	Schiller et al, 1970 ¹⁶	—	—	Vulvar lesion	—	Unknown	DLCL (Reticulum cell sarcoma)	—	—

Continued

Table I. Cont'd

Patient number	Reference	Age	PMH	Clinical presentation	Size	Ann Arbor stage	Histopathology	Initial treatment	Outcomes
20	Iliya et al, 1968 ¹⁷	75	—	Mass	3 cm	Unknown	DLCL (reticulum cell sarcoma)	Excision	AWOD at 5 y
21	Buckingham & McClure, 1955 ¹⁸	33	African American, nulligravida	2-wk history of rapidly enlarging, ulcerated mass; 50-lb weight loss over unknown period	14 cm	Unknown	DLCL (reticulum cell sarcoma or lymphosarcoma)	Local excision and RT with partial response	AWD at 6 mo
22	Taussig, 1937 ¹⁹	63	Multiparous	8-mo history of enlarging, nontender mass with overlying ulceration and associated bleeding, weight loss of 8 lb over previous year	2 × 1.5 cm	Unknown	DLCL (lymphosarcoma)	Local excision	Died 15 days post-op due to presumptive PE

AWD, Alive with disease; AWOD, alive without disease; CR, complete remission; CT, chemotherapy; DLBCL, diffuse large B-cell lymphoma; DLCL, diffuse large cell lymphoma; DOD, died of disease; DWD, died with disease; PCDLBCL-LT, primary cutaneous diffuse large B-cell lymphoma – leg type; PCDLBCL (NOS), primary cutaneous diffuse large B-cell lymphoma – not otherwise specified; PMH, past medical history; PROVECIP, vinblastine, procarbazine, prednisone; RT, radiation therapy; SO, salpingo-oophorectomy; TAH, total abdominal hysterectomy.

analysis and application of now obsolete classifications; nevertheless, some clues as to the nature of the condition emerge in the context of known cases. Search of PubMed/Medline English-language literature databases identified 20 additional cases of apparent localized vulvar masses with DLBCL or likely DLBCL diagnosis (stage I/II) (Table I).

Based on our case review, primary vulvar DLBCL is a condition affecting women with a mean age of 58, a median age of 64, range of 25 to 79, bimodally distributed between 25 and 43 and 61 to 79, with an average length of follow-up of 28 months (Table D). Based on 20 of 22 cases of vulvar DLBCL that reported clinical presentations, 8 of 20 cases (40%) presented with ulceration, 30% with enlarging mass, and 25% with nontender mass. Pruritus, erythema, and edema have also been described.

When placed in the context of prior reported cases of primary vulvar DLBCL, our cases appear to fit a larger narrative of frequently treatment-responsive disease with good initial prognosis (Table I). Generally, management of primary vulvar DLBCL has included excision, radiotherapy, and chemotherapy, each alone and in combination, without clear superiority of any specific therapeutic intervention. Including the current cases, of the 22 patients reviewed in the literature, 2 are reported to have died of disease. One was a 25-year-old HIV-positive woman presenting with an ulcerated large (up to 12 cm) mass with concurrent weight loss. She had stage IE disease that did not respond to low-dose cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP)-bleomycin and only partially responded to radiotherapy. The patient died 7 months after diagnosis.¹² The other was a 67-year-old woman with stage IIE DLBCL manifesting as a pruritic mass that achieved complete response with chemotherapy and radiation therapy. The disease was followed by recurrence in the spine, and the patient died 2 years after the initial diagnosis.³ Dissecting the data further, the 25-year-old woman who died of disease represented 1 of 2 patients who experienced only a partial response to therapy, comprising 12.5% of the total cases with reported outcomes (2 of 16). Both of these partial-response patients were notably younger and African American and had bulky, ulcerated tumors of 10 cm or larger, features which may portend adverse prognosis.

Of note, the vulva, situated at a unique interface between skin and mucosal lymphoid tissue, represents a site of DLBCL presentation whose accurate categorization as primary cutaneous or nodal is

uncertain. Our 2 additional patients, reviewed in the context of the available literature, add to the characterization of vulvar DLBCL as a lymphoma affecting a broad age range, with variably nodular presentations, and with a generally good initial response to treatment.

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