Vulvar involvement in epidermolysis bullosa: Case series

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Key words: epidermolysis bullosa; vulvar.

INTRODUCTION

Epidermolysis bullosa (EB) comprises a rare group of inherited disorders that present with blistering of the skin and mucous membranes. It is classified into 4 types according to the plane of cleavage. Epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), dystrophic epidermolysis bullosa (DEB), and Kindler syndrome present with blisters in different ultrastructural sites: intraepidermal, intralamina lucida, sublamina densa, and mixed, respectively (Fig 1).[1] To date, no study has addressed the clinical aspects and management of EB when it affects the vulva. Skin fragility is a significant issue in these patients and is a particular challenge for genital skin. It can significantly affect the quality of life, especially the psychosexual aspect. This case series sought to identify and describe clinical, functional, and psychosexual issues related to vulvar involvement in women with EB as well as their treatment. We report the cases of 6 women and 5 juvenile patients diagnosed with EB who were followed by our Multidisciplinary Epidermolysis Bullosa Team of the Centre Hospitalier de L'Université de Montréal (for adults) and the Centre Hospitalier Universitaire Sainte-Justine (for pediatric patients). The team includes a network of specialists in different fields, such as dermatology, gynecology, otorhinolaryngology, gastroenterology, dentistry, physiotherapy, and sexology.

Consent was obtained for publication of the patients' cases.

CASE SERIES

The characteristics and treatments of the patients are presented in Tables I and II.

Abbreviations used:

DDEB:	dominant dystrophic epidermolysis bullosa
DEB:	dystrophic epidermolysis bullosa
EB:	epidermolysis bullosa
EBS:	epidermolysis bullosa simplex
HSIL:	high-grade squamous intraepithelial lesion
JEB:	junctional epidermolysis bullosa
LSIL:	low-grade squamous intraepithelial lesion
RDEB:	recessive dystrophic epidermolysis bullosa

Case 1

Patient 1 had recessive dystrophic epidermolysis bullosa (RDEB), generalized intermediate. She had suffered from superficial dyspareunia since her first sexual intercourse. She had recurrent painful fissures and bleeding of the vulvar fourchette and anal areas and constipation. She was unable to use tampons. Physical examination showed a vulvar fissure at the fourchette area and an anal fissure. Local treatments included topical 2% lidocaine jelly and petroleum jelly applications (particularly before and after defecation and before micturition). Silicone-based lubricants were recommended for intercourse. Pelviperineal physiotherapy had helped for treatment of dyspareunia.

Case 2

Patient 2 had JEB, generalized intermediate. She had suffered from superficial dyspareunia since her first sexual intercourse. Vaginismus and labial synechiae developed over time. She had recurrent painful fissures and bleeding of the anal area. Physical examination showed fissures involving the

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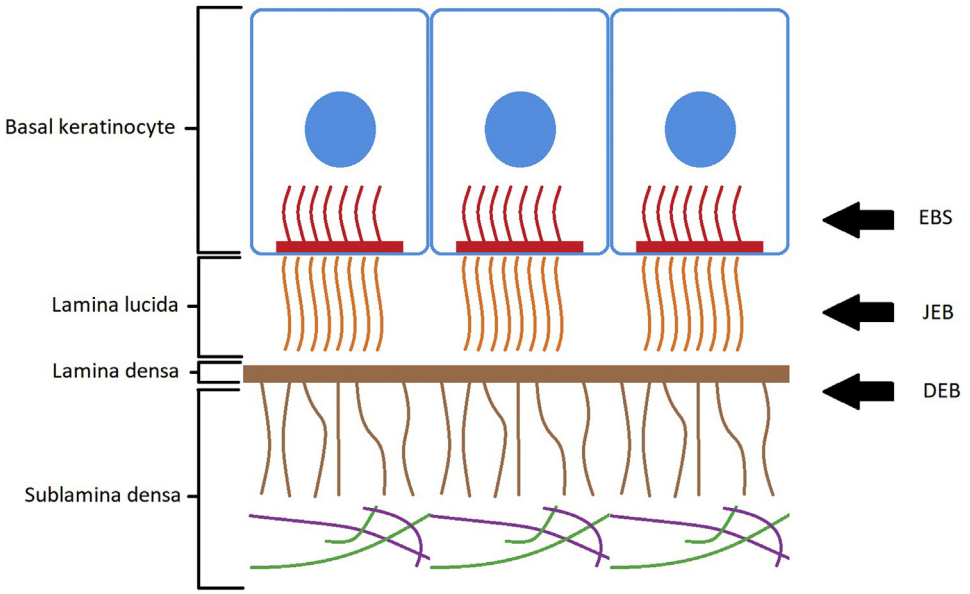

Fig 1. Planes of cleavage for each epidermolysis bullosa subtype. *DEB*, Dystrophic epidermolysis bullosa; *EBS*, epidermolysis bullosa simplex; *JEB*, junctional epidermolysis bullosa.

anterior aspect of the anal margin, posterior labial fusion of the labia minora on the labia majora, and bridging of the fourchette area. Over the years, treatments focused on relieving constipation and dealing with dyspareunia, perineal pain, and vaginismus.

Case 3

Patient 3 had RDEB, generalized intermediate. She had suffered from superficial dyspareunia since her first sexual intercourse. Vaginismus and labial synechiae developed over time. Additionally, she had recurrent painful fissures and bleeding of the fourchette and anal areas. Physical examination showed bridging of the fourchette area and fissures involving the posterior aspect of the anal margin (Fig 2). She had significant tenderness of the vestibular area. Over the years, treatments focused on relieving constipation and dealing with dyspareunia, perineal pain, and vaginismus.

Case 4

Patient 4 had RDEB, generalized intermediate. She had suffered from superficial dyspareunia since her first sexual intercourse. She had never had issues with tampons. She described vaginal discharge after intercourse as resembling "sheets of skin." Physical examination showed whitish lichenified plaques and recurrent anterior anal fissures extending to the perineum as well as anterior and posterior bridging of the vestibule (Figs 3 and 4). A vulvar biopsy revealed a paucicellular subepidermal blister, compatible with EB, and no lichenoid changes. Over the years, treatments focused on relieving constipation and dealing with dyspareunia.

Case 5

Patient 5 had EBS. She had whitish lichenified plaques of the labia majora and posterior aspect of the buttocks (Fig 5), in which 2 biopsies showed degeneration of basal keratinocytes, with suprabasal and subepidermal acantholysis, confirming EB with no evidence of lichen sclerosus. She also had a perineal high-grade squamous intraepithelial lesion (HSIL) induced by human papillomavirus (Fig 6).[2] She did not have dyspareunia, vaginismus, constipation, or vulvar or anal erosions or fissures.

Case 6

Patient 6 is the daughter of patient 5. She had EBS. She is the only adult patient who has had no vulvar symptoms, with a completely normal examination. She had never been sexually active. However, she had constipation and reported anal fissures, which were partially relieved by laxatives.

Juvenile patients

Four prepubescent children with EB were evaluated. Two children had EBS, one had dominant dystrophic epidermolysis bullosa (DDEB), and one had possible DEB, awaiting confirmation of the genetic mutation(s). None of them presented with vulvar or anal lesions. One 14-year-old patient with

Table I. Patient demographics and characteristics

Patient	1	2	3	4	5	6
Age, y	27	30	24	24	51	27
Ethnicity	French Canadian	Sri Lankan	French Canadian	French Canadian	English Canadian	English and French Canadian
EB type	RDEB, generalized intermediate	JEB, generalized intermediate	RDEB, generalized intermediate	RDEB, generalized intermediate	EBS	EBS
Family history	Father carrier Mother had VUS on IVS73-4delT	Both parents carriers	Mother carrier Father had VUS on c.6181-4delT	Mother and maternal grandmother carriers Father: no mutation found in 2002	Father carrier Daughter with EB (patient 6)	Mother (patient 5) and grandfather carriers
Genetic mutation	*COL7A1* 2 heterozygous mutations in p.Gly575Arg heterozygous VUS IVS73-4delT	*COL17A1* homozygous c418_419del (p.Ser140*) heterozygous VUS c.4720C>T (p.Arg1574Trp) *PLEC* heterozygous VUS c.7715G>A (p.Arg2572Gln)	*COL17A1* heterozygous 2728delC heterozygous VUS c.6181-4delT	*COL7A1* (details not found)	*KRT14* heterozygous c.380_391 del12 (p.Ala 127_leu130del)	*KRT14* heterozygous c.380_391 del12 (p.Ala 127_leu130del) *PLEC* heterozygous VUS c5173C>T (p.Arg 1725Trp)
Clinical manifestations						
Skin	Occasional bullae posttrauma, Bart syndrome in infancy	Severe, since birth, bullae and erosions on trunk and extremities, plantar hyperkeratosis, dystrophy, dyskeratotic acanthomas, cicatricial alopecia	Occasional bullae on lower limbs posttrauma during childhood. No bullae since adulthood. Occasional pruritus. Anonychia, ungual dystrophia	Occasional bullae on lower limbs posttrauma, erythematous plaques, and milia	Occasional bullae on lower limbs posttrauma, palmo-plantar keratoderma, ungual dystrophy	Multiple bullae on body, palmo-plantar keratoderma, ungual dystrophy
Ocular	None	None	None	Bilateral symblepharons of the external canthus	None	Anterior blepharitis not related to EB
Oral	Ulcers, gingivitis, delay in tooth eruption, cavities	Rare bullae, gingivitis	Chronic moderate desquamative gingivitis, occasional bullae, loss of anterior vestibule	Erosive gingivitis, rare bullae	Bullae during childhood, palatine infections	Occasional dysphagia, cheilitis
Esophageal	Strictures, webs	None	Esophageal diaphragm	Esophageal stenosis	Acid reflux	Acid reflux

Continued

Table I. Cont'd

Patient	1	2	3	4	5	6
Skin treatment	Topical antibiotics,* petroleum jelly, wound care†	Topical treatments: medium-potency corticosteroids, antibiotics,* ketamine 2%, lidocaine 10%, nifedipine 0.2% morphine 0,1%, baclofen 2%, petroleum jelly, keratolytics‡ for hands and feet, wound care.† Pregabalin 50 mg orally once daily Plantar orthoses	Topical antibiotics,* petroleum jelly	Medium- and high-potency topical corticosteroids, petroleum jelly, wound care†	Topical keratolytics‡ for hands and feet, petroleum jelly, wound care†	Topical antibiotics,* topical keratolytics‡ for hands and feet, petroleum jelly, wound care†

EB, Epidermolysis bullosa; *EBS*, epidermolysis bullosa simplex; *JEB*, junctional epidermolysis bullosa; *RDEB*, recessive dystrophic epidermolysis bullosa; *VUS*, variant of unknown significance.
*Topical antibiotics used included bacitracin/polymyxin B, 2% fusidic acid, and 2% mupirocin.
†Wound care used included nonadherent foam and silicone dressings.
‡Topical keratolytics used included 20% to 40% urea and 20% to 30% salicylic acid.

DEB was also evaluated. She was sexually active and did not have any vulvar or anal lesions.

Psychosexual distress

A 3-item sexual distress questionnaire was administered to assess the presence of sexual distress: how often did the patient feel she was distressed about her sex life, inferior because of sexual problems, and worried about sex. This concise questionnaire showed the presence of sexual distress in all patients for at least 2 of the 3 items. Further evaluations are planned, as well as counseling with a sexologist.

DISCUSSION

Five of our 6 adult patients had vulvar and anal involvement related to EB that impacted their quality of life. Interestingly, this was not the case for our 5 juvenile patients. Genital biopsies were performed only in the presence of whitish plaques to exclude other diagnoses, such as lichen sclerosus and lichen planus. They confirmed EB for patients 4 and 5. When only genital fissures were present, biopsies were not performed, and the lesions were attributed to EB based on the clinical overall presentation and previous skin biopsies confirming EB. No cases in the literature have described concomitant lichen sclerosus or other vulvar bullous diseases in the context of inherited EB.

For all postpubescent women with EB, specific questions need to be asked to identify psychosexual and anogenital issues: menses (use of tampons or sanitary pads), concerns about sexual intercourse, number of stools per week, vulvar or anal pain or blood during micturition or stool passage, quality of life, and others. Dyspareunia was the most common symptom (4 of 6 patients) because of skin friction and peeling during sexual intercourse. We recommend a silicone-based lubricant during sexual intercourse and 2% or 5% topical xylocaine before and after sexual intercourse. Synechiae, erosions, and fissures are also common findings that mainly affect the vulva and perineum but spare the vagina. The perineum is a particularly sensitive region. Pressure and friction are more important in this area, especially during sexual intercourse. The pelvic floor muscles, such as the transverse perineal muscle, can become tighter because of the pain, leading to increased tension on the perineal skin. Anal lesions, mostly erosions and fissures, can lead to constipation (5 of 6 patients). Appropriate preventive measures, such as a barrier cream or

Table II. Vulvar and anal involvement

Patient	1	2	3	4	5	6
Vulvar	Dyspareunia, erosions, fissures	Dyspareunia, vaginismus, labial synechiae	Dyspareunia, vaginismus, synechiae, fissures, vestibular pain	Dyspareunia, vaginismus, perineal pain, erosions, fissures, vaginal discharge Biopsy-proven EB with no evidence of lichen sclerosus	Biopsy-proven EB with no evidence of lichen sclerosus Perineal HSIL	Normal
Papanicolaou and vaginal smears	Normal	Normal	Normal	Normal	Papanicolaou test: LSIL	
Obstetric	G1P1A0, elective cesarean section	G1P1A0, elective cesarean section	G0	G0	G3P2A1: 1 spontaneous abortion, 2 normal vaginal deliveries	G0
Anal	Constipation, erosions, fissures	Constipation, pruritus, fissures	Constipation, erosions, fissures	Constipation, fissures	Condyloma	Constipation, fissures
Vulvar/anal treatment	Topical lidocaine 5%, petroleum jelly, silicone-based lubricants, pelviperineal physiotherapy	Low-potency topical corticosteroids, clotrimazole 1%, silicone-based lubricants, pelviperineal physiotherapy	Topical morphine 0.1%, petroleum jelly, silicone-based lubricants, pelviperineal physiotherapy, sexology consultation For perianal: glycerin, petrolatum, phenylephrine hydrochloride 0.25%, pramoxine hydrochloride 1% cream	Low-potency topical corticosteroids, clotrimazole 1%, topical estrogen, petroleum jelly, silicone-based lubricants, pelviperineal physiotherapy, sexology consultation	Medium- and high-potency topical corticosteroids Surgical removal for HSIL	None
Synthetic progestins and oral contraceptives use	Ethinyl estradiol 0.6 mg and norelgestromin 0.6 mg, transdermal patch × 3 y	None	Ethinyl estradiol 0.6 mg and norelgestromin 0.6 mg, transdermal patch × 6 y Then medroxyprogesterone 150 mg injection × 1 y	Oral ethinyl estradiol 25 μg/norgestimate 180 μg × 1 y Then oral ethinyl estradiol 25 μg/cyproterone 2 mg × 7 y	None	Medroxyprogesterone 150 mg injection × 5 mo Then oral ethinyl estradiol 25 μg/levonorgestrel 100 μg × 3 y Then norethindrone 0.35 mg × 1 mo

EB, Epidermolysis bullosa; *HSIL*, high-grade squamous intraepithelial lesion; *LSIL*, low-grade squamous intraepithelial lesion.

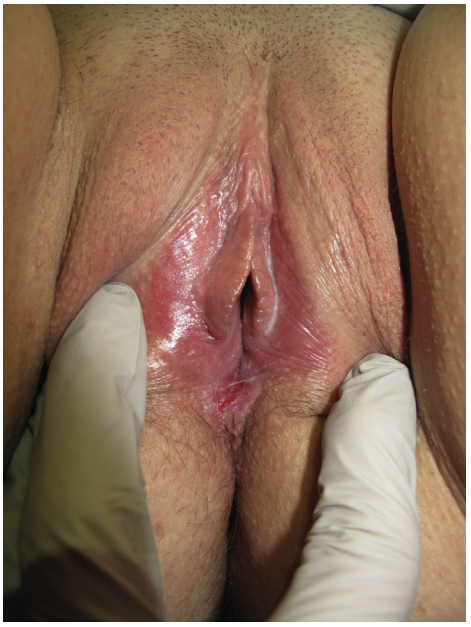

Fig 2. Patient 3: erosions, fissures, and bridging of the posterior aspect of the fourchette.

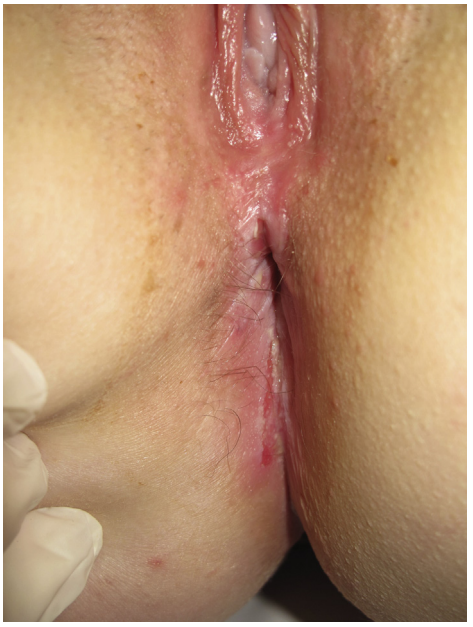

Fig 4. Patient 4: erythematous and white perineal and perianal fissured plaques.

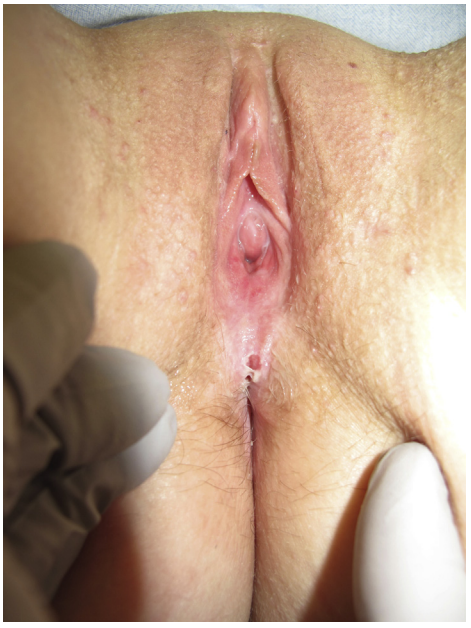

Fig 3. Patient 4: posterior labial fusion of labia minora on labia majora, white fissured plaque of perineum, and anterior anal fissure.

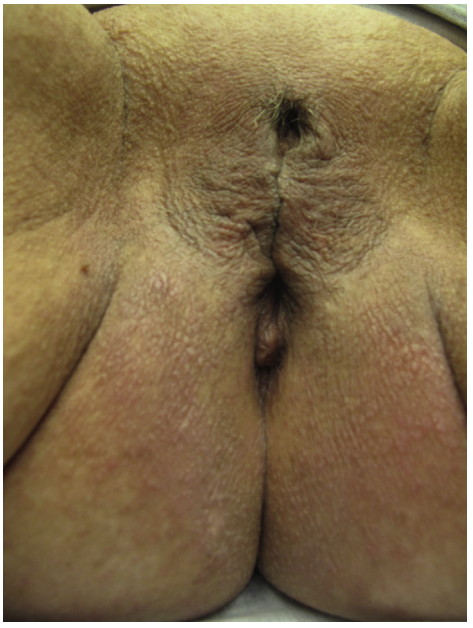

Fig 5. Patient 5: whitish lichenified plaques of the labia majora and posterior aspect of the buttocks.

petroleum jelly before micturition and before and after defecation, topical corticosteroids, and analgesics, can help manage symptoms. Pelviperineal physiotherapy is particularly beneficial in addressing dyspareunia and vaginismus in patients dealing with these issues. A sexology consultation, which provides counseling intended to help individuals and couples resolve sexual difficulties, is also recommended to help deal with psychosexual issues.

Four patients had normal Papanicolaou smears. One patient had a Papanicolaou smear suggesting a low-grade squamous intraepithelial lesion (LSIL) and a perineal biopsy showing an HSIL. Two patients had elective cesarean sections, even though vaginal deliveries were not contraindicated for them. One

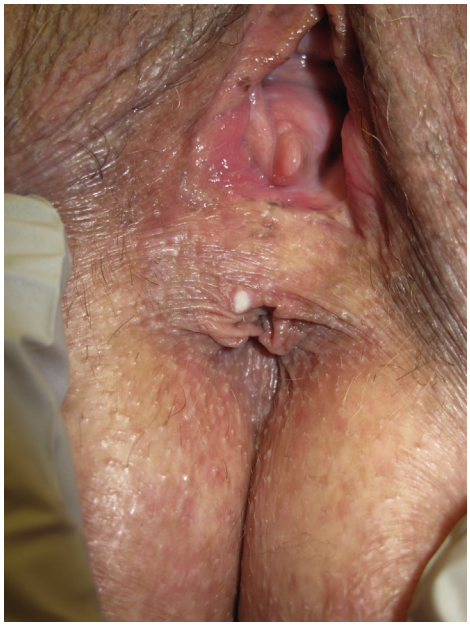

Fig 6. Patient 5: a white millimetric papule at the anterior aspect of the anus, histologically compatible with high-grade squamous intraepithelial lesion.

patient had 2 normal vaginal deliveries. A review of the literature showed that normal vaginal deliveries appear to be safe in patients with EB, without any increased risk of pregnancy-related complications.[3,4] Our limited experience is consistent with this, but a case-by-case evaluation is recommended.

All our patients had their quality of life impacted in part by their psychosexual issues. As reported in the literature, quality of life is significantly affected in patients with EB.[5] Psychosexual issues play an important part in this impact. We recommend having an open discussion with the patient about any psychosexual issues she may be facing and involving a sexologist and/or psychologist if needed.

In conclusion, vulvar, anal, and perianal involvement is a common finding among postpubescent women with EB and can significantly impact their quality of life. To our knowledge, this is the first study addressing this aspect as well as its management. Dyspareunia is the most common finding. Synechiae, erosions, and fissures can also be significantly symptomatic. Anal involvement, characterized by constipation, erosions, and fissures, is also frequently found. All 6 of our adult patients had psychosexual distress, including the patient with a completely normal vulvar examination. These findings indicate the need to address vulvar, anal, and psychosexual issues in every postpubescent woman to avoid delay in treatment. Initiating appropriate preventive measures (silicone-based lubricant, local topical lidocaine, and barrier cream or petroleum jelly), treatments, and pelviperineal physiotherapy can help manage symptoms. A sexology consultation is strongly recommended to help deal with the psychosexual aspect of EB.

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Conflicts of interest

None disclosed.

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