Juvenile and adult vulvar pemphigoid, an under recognized entity: Case series of fourteen patients

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INTRODUCTION

Vulvar pemphigoid (VP) is a rare subtype of mucous membrane pemphigoid (MMP), which is a heterogeneous group of autoimmune subepidermal blistering diseases with predominantly mucosal involvement and characterized by autoantibodies against structural proteins in the epidermal basement membrane zone (EBMZ).[1] In MMP, various mucosal sites can be simultaneously or separately affected. Mucosal lesions tend to heal with scar formation and may result in loss of function of the affected area.

In vulvar MMP, lesions are confined to the anogenital region but can also be a manifestation of a more extensive MMP with other mucosal involvement.[2-5] Two variants can be distinguished: the juvenile form presenting in girls between 5 and 10 years old, and the adult form, which occurs mainly in postmenopausal women.[6,7] However, symptoms may also occur in patients within these two age categories. Overlapping with other chronic vulvar diseases, VP can present with variable clinical and histopathologic features, including lichen sclerosus (LS) and erosive lichen planus affecting the vulva (ELPV).[8,9] Careful examination of the mucosa and skin is mandatory, which should be followed by a biopsy for direct immunofluorescence microscopy (DIF) from perilesional skin or mucosa. Furthermore, indirect immunofluorescence microscopy (IIF) on salt split skin (SSS) and immunoserology can be performed for the detection of circulating autoantibodies in serum.

Abbreviations used:

DIF:	direct immunofluorescence microscopy
EBMZ:	epidermal basement membrane zone
ELPV:	erosive lichen planus affecting the vulva
LS:	lichen sclerosus
MMP:	mucous membrane pemphigoid
VP:	vulvar pemphigoid
SSS:	salt split skin
IIF:	indirect immunofluorescence microscopy
ELISA:	enzyme-linked immunosorbent assay
C3c:	complement component 3
Ig:	immunoglobulin

In this study, we describe 14 patients diagnosed with VP, demonstrating the wide clinical and immunologic variety of this disease.

METHODS

This case series included patients diagnosed with VP from 2001 to 2018 at the Center for Blistering Diseases in Groningen, which is the national referral center for autoimmune bullous diseases in the Netherlands. Diagnoses were made according to clinical features and immunologic criteria of linear n-serrated/u-serrated deposition of IgG, IgA, and/or complement component 3 along the EBMZ by DIF or detection of circulating autoantibodies. IIF on SSS was considered positive when immunoglobulin (Ig)G, IgA, and/or complement component 3 (C3c) staining at the epidermal and/or dermal side staining were observed. Immunoblot was used to detect

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Table I. Clinical characteristics, diagnostic results, and treatment of patients with vulvar pemphigoid

Patient no.	Age in years	Symptom duration in months	Scarring	Other mucosal involvement	Skin involvement	Histopathology	DIF on mucosa and/or skin	Salt split skin	Immunoblot	ELISA NC16A	Topical therapy	Systemic therapy
1	5	12	Yes	-	-	Vacuolar degeneration basal keratinocytes, homogenized collagen	IgG & C3c	Negative	IgG BP180	Negative	Clobetasol, Tetracycline	Prednisone, Dapsone
2	6	6	No	-	-	Ulcerating inflammation, subepidermal split	IgG & C3c	Negative	Negative	Negative	Triamcinolone, Tetracycline	-
3	11	30	Yes	Oral	-	Dermal mixed cell inflammation, subepidermal split	C3c	IgG epidermal side	IgG BP180	Negative	Tetracycline	-
4	11	72	No	-	-	Dermal mixed cell inflammation, subepidermal split	IgG & IgA & C3c	Negative	Negative	Positive	Tetracycline, Triamcinolone	Dapsone
5	12	24	No	-	-	Band-like lymphocytic infiltrates, subepidermal split	IgG & C3c	Negative	Negative	Negative	Tetracycline, Clobetasol	-
6	13	7	No	-	-	Dermal mixed cell inflammation, subepidermal split	IgG & IgA & C3c	Negative	Negative	Positive	Tetracycline	-
7	48	9	Yes	Oral	-	dermal lymphohistiocytic inflammation, subepidermal split	IgG & C3c	Negative	IgG BP180	Negative	Tetracycline, Clobetasol, Triamcinolone	Doxycyline, Prednisone
8	58	12	Yes	-	Submammary	Dermal mixed cell inflammation, subepidermal split	IgG, IgA & C3c n-serrated	IgG & IgA epidermal side	IgG BP180	Positive	Triamcinolone	Prednisone, Dapsone, Mycophenolic acid, Cyclophosphamide, Rituximab
9	62	12	No	-	-	Dermal lymphoplasmacellular inflammation, subepidermal split	C3c n-serrated	Negative	IgG BP180	Positive	Triamcinolone, Fluticasone, Clobetason, Tetracycline	Doxycycline
10	65	60	Yes	-	-	Dermal mixed cell inflammation, subepidermal split	IgG, IgA & C3c	IgG epidermal side	IgG & IgA BP180	Positive	Clobetasol Tetracycline	Prednisone, Methotrexate, Mycophenolic acid, Azathioprine
11	73	2	No	Oral	-	-	IgG	Negative	Negative	Positive	Tetracycline	-

12	74	5	No	Oral	-	Perivascular lymphoplasmacellular inflammation	IgA	IgA epidermal side	IgA BP180	Negative	Tetracycline, Triamcinolone	Dapsone
13	74	14	Yes	Oral	-	Superficial spongiotic dermatitis	IgG n-serrated	IgG epidermal side	Negative	Negative	Clobetasol	-
14	91	7	Yes	Oral, nasal	-	Subepidermal split	IgA, IgG n-serrated	IgG epidermal side	IgG BP180	Positive	Clobetasol	Cyclophosphamide

DIF, Direct immunofluorescence microscopy; *ELISA*, enzyme-linked immunosorbent assay; *Igg*, immunoglobulin; *C3c*, complement component 3.

circulating IgG or IgA against BP180. Autoantibodies against the 16A domain of BP180 were detected with commercially available enzyme-linked immunosorbent assay (ELISA; cutoff index, ≥ 9 U/mL). Written consent was provided.

RESULTS

Fourteen patients diagnosed with VP were included in this case series. One patient was previously described in the literature.[10] Table I summarizes the clinical, histopathologic, and immunofluorescence findings, as well as the prescribed therapy of all patients. Six patients were diagnosed with juvenile VP, and the remaining 8 were postmenopausal women. The age of onset ranged between 5 and 13 years in the juvenile group, and 48 and 91 years in the adult group. The median duration of symptoms before patients were referred to the dermatologist at the Center for Blistering Diseases was 12 months (range, 2-72). Patients with extragenital involvement had a shorter median diagnostic delay compared with patients with localized genital involvement (8 *vs.* 12 months). The median follow-up time was 22 months (range, 1-86). At the time of referral, 3 patients had already received the diagnosis VP. One patient had previously been diagnosed with LS based on clinical and histologic features, and 1 patient had been diagnosed with vulvar candidiasis. The remaining patients were referred to our clinic with no previous diagnosis.

Clinical presentation

Frequently reported symptoms included intermittent or continuous pain (10/14), followed by pruritus (5/14) and dysuria (5/14). Dyspareunia was reported in 1 adult patient, and 2 patients experienced pain during defecation. One patient in the juvenile group was asymptomatic. Dermatologic examination revealed erosions (11/14), erythema (9/14), and superficial ulcerations (2/14) of the labia minora and majora, periclitoreal area, vaginal introitus, and perineum (Fig 1, *A, B* and *C*). In one patient, an intact blister was seen. Structural architecture loss was observed in 5 adult patients, including fusion of the labia majora and minora and stenosis of the vaginal introitus, whereas only 2 patients in the juvenile group developed fusion of the labia (Fig 1, *B* and *C*). Examination of the vaginal mucosa was not performed. Extragenital mucosal involvement was seen in 6/14 patients, of which 1 patient in the juvenile group presented with erythematous swollen gingiva and 5 adult patients with erythema, erosions, and blisters involving the gingiva, palatal surface, and buccal mucosa. One patient presented with

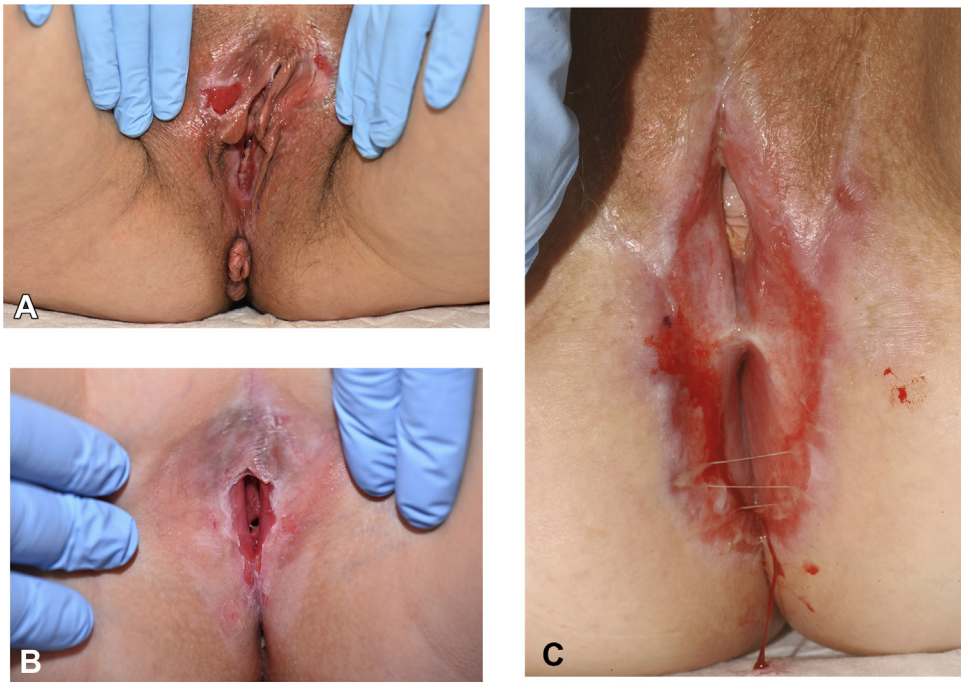

Fig 1. Lesions in juvenile and adult vulvar pemphigoid demonstrating erosions (**A** and **C**), scar formation (**B** and **C**), and complete fusion of the labia (**B** and **C**).

nasal crustae in addition to involvement of the oral mucosa. Furthermore, 1 adult patient had skin involvement confined to the submammary region.

Diagnostic findings

In all patients (14/14), a biopsy for DIF was performed from perilesional mucosa and/or healthy skin, revealing linear deposition of IgG, IgA, and/or C3c complement component 3 along the EBMZ (Fig 2, *A*). An n-serrated immunodeposition pattern along the EBMZ was identified in 4/14 biopsies for DIF, and in the remaining biopsies the serration pattern could not be identified. IIF on SSS revealed circulating IgG and/or IgA autoantibodies in 6/14 patients at the epidermal side of the split (Fig 2, *B*). Immunoblot for BP180 was positive for IgG and/or IgA in 8/14 patients, and 7/14 patients showed positivity for IgG against the NC16A domain of BP180, as detected by ELISA. A biopsy for histopathology was performed in 13/14 patients, revealing subepidermal blistering in 10 patients accompanied with a dermal infiltrate consisting of lymphocytes, plasma cells, and eosinophils. One patient showed a band-like infiltrate of lymphocytes at the epidermal-dermal junction; furthermore, in 1 patient, basal vacuolar degeneration and homogenization of the dermal collagen was observed. Bacterial, fungal, and viral cultures were negative for all patients.

Therapy

After confirmation of the diagnosis, 8/14 patients required systemic immunosuppressive or immunomodulatory therapy in addition to local therapy. In the juvenile group, 2/6 patients received dapsone in addition to local therapy, while 4/6 patients received only topical corticosteroids. In 1 patient, dapsone was discontinued after 1 year due to hemolysis and replaced by prednisone followed by topical clobetasol propionate. Flare-ups were frequently observed during treatment in this patient. The clinical outcome of the second patient is unknown, as follow-up took place in another hospital after the diagnosis was made. The remaining 4 patients in the juvenile group responded well to topical triamcinolone acetonide and clobetasol only and did not experience flare-ups during treatment. The median duration until clinical response was 2 months (range 0-28) in the juvenile group.

Six out of 8 patients in the adult group required systemic immunosuppressive therapy due to worsening of vulvar symptoms and poor response to local therapy. Systemic treatment included doxycycline, prednisone, dapsone, methotrexate, azathioprine, cyclophosphamide, mycophenolic acid, and rituximab. The median duration until clinical response was 1.5 months (range, 0-18). Flare-ups were seen in 5 out of 8 patients during treatment. These patients received several systemic

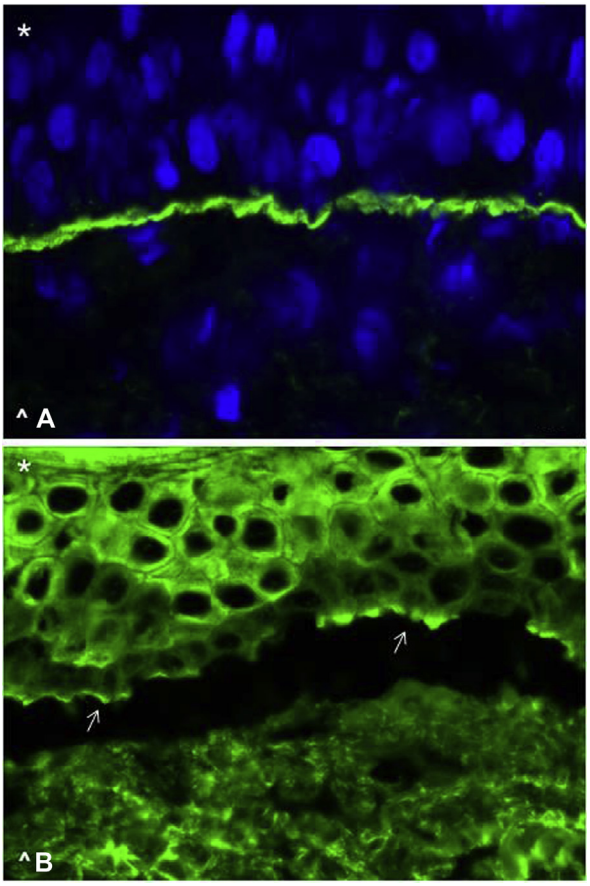

Fig 2. A, Direct immunofluorescence microscopy showing linear C3c deposition along the epidermal basement membrane zone in an n-serrated pattern. **B,** Indirect immunofluorescence on a substrate of salt split skin, showing IgG bound to the epidermal basement membrane zone (*arrow*) of the artificial split. The epidermal side is depicted with * and the dermal side is depicted with ^.

immunosuppressive agents during follow-up. The remaining 2 patients who were treated with topical treatment only did not experience flare-ups during treatment.

DISCUSSION

This case series of 14 patients with juvenile and adult VP demonstrates the broad clinical spectrum of this disease. In the presence of vulvar erosions, ulcerations, blisters, and scarring, VP should be considered in the differential diagnosis. In addition, examining extragenital mucosal surfaces and performing immunofluorescence microscopy and immunoserology is mandatory to differentiate between conditions with similar clinical findings.

VP is often misdiagnosed for LS or ELPV, resulting in therapeutic delay.[8,10] In children, VP may also be mistaken for sexual abuse.[11] Differentiating between LS, ELPV, and VP is often challenging due to overlapping clinical presentation and the presence of chronic inflammation. The presence of Wickham striae, patchy hair loss, or nail abnormalities can distinguish lichen planus from pemphigoid. Vaginal involvement is common in ELVP but has not been previously reported in VP.[4,5,12] In this study, examination of the vaginal mucosa was not performed. However, patients diagnosed with VP should be examined by a gynecologist with expertise in ELVP for evaluation of vaginal involvement. In contrast to LS, MMP and ELPV may affect other mucosal sites, such as the ocular, nasal, pharyngeal, and laryngeal mucosa. In this study, the presence of extragenital involvement might have led to a quicker diagnosis. Extragenital involvement, including the oral and nasal mucosa, was observed more often in the adult group. In addition, more patients in the adult group presented with scar formation.

Histopathology can often be used to differentiate VP from ELVP and LS. However, in some cases, histologic differences are not that clear and may overlap. A lesional biopsy for histopathology in pemphigoid can show subepidermal splitting combined with a moderate to dense infiltrate composed of lymphocytes, neutrophils, and eosinophils. This can also be seen in bullous LS, which is caused by either increased vacuolar degeneration of the basal membrane zone or edema in the papillary dermis.[13,14] In this study, a subepidermal split was seen in 10 patients. Moreover, histopathologic features mimicking lichen planus and LS were observed.

Overall, VP of the juvenile form responds promptly to potent topical therapy and generally does not require systemic therapy. In the juvenile group, 4 out of 6 patients had relatively mild disease and responded well to potent topical steroids, with the exception of 2 patients, who were treated with systemic corticosteroids and dapsone. In contrast, the majority of the adult patients required systemic therapy and often showed flare-ups.

In conclusion, VP presents a broad spectrum of symptoms and can be challenging to diagnose. Performing careful examination of other mucosae and skin with additional immunofluorescence and immunoserology is essential for an adequate diagnosis.

Conflicts of interest

Dr Horváth reports fees from Janssen-Cilag (Advisory Boards, Educational grants, Consultations, Investigator

Initiative Studies), AbbVie (Advisory Boards, Educational grants, Consultations, Investigator Initiative Studies), Novartis Pharma (Advisory Boards, Consultations, Investigator Initiative Studies), UCB Pharma (Advisory Boards, Consultations), Leo Pharma (Consultations), Solenne B.V. (Investigator Initiative Studies), Celgene (Consultations, Investigator Initiative Studies), Akari therapeutics (Consultations, Investigator Initiative Studies), Philips (Consultation), Roche (Consultation), Regeneron (Consultation) and Sanofi (Consultation), which fees were paid to the institution. The remaining authors declare no conflict of interest.

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