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 immunoblot can be performed for the detection of circulating autoantibodies in serum.

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 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
| 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 | 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 | Doxycycline, 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, Fluticasone, Clobetasol, Tetracycline | Prednisone, Dapsone, Mycophenolic acid, Cyclophosphamide, Rituximab | Doxycycline |
| 9          | 62           | 12                        | No       | -                        | -               | Dermal lymphoplasmacellular inflammation, subepidermal split | C3c n-serrated | Negative | IgG BP180 | Positive | Triamcinolone, Fluticasone, Clobetasol, 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 | - |
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. 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. Extragénital 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
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
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. Patients 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 mucosal and skin with additional immunofluorescence and immunoserology is essential for an adequate diagnosis.

Conflicts of interest

Dr Horváth reports fees from Janssen-Cigna (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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