Vulvo-cervico-vaginal manifestations and evaluation of Papanicolaou smears in pemphigus vulgaris and pemphigus foliaceus

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Background: Vulvo-cervico-vaginal involvement has rarely been reported in pemphigus vulgaris (PV) and has not been reported in pemphigus foliaceus (PF).

Objectives: We sought to evaluate genital lesions and Papanicolaou (Pap) smears in female patients with PV and PF.

Methods: This prospective study includes all consecutive cases of female patients with PV and PF seen from May 2009 to February 2010. Gynecologic examination was performed and Pap smears were collected for cytologic analysis from each patient.

Results: A total of 56 patients were given a diagnosis of pemphigus (41 PV and 15 PF). Genital involvement was observed in 9 patients with PV (22%) and the vulva was the most common genital site of involvement. Of these 9 patients, 8 presented with active skin/mucous lesions. Four of 15 patients with PF had genital lesions and vulva was the exclusive site of involvement. Three of 4 patients with PF and genital involvement also showed active cutaneous lesions. Six of 56 patients (5 PV and 1 PF) presented with atypical squamous cells of undetermined significance in Pap smear analysis. Upon further pathologic review, acantholytic cells were seen, confirming the diagnosis of pemphigus.

Limitations: A small number of PF cases were studied.

Conclusions: Vulvar lesions were the second most frequent site of mucous membrane PV. Herein we report the first case to our knowledge of symptomatic genital lesions in a patient with PF. Moreover, acantholytic cells in Pap smears were found in a patient with PF who was in complete remission off therapy with no clinical genital lesions and no circulating anti-desmoglein-1 and anti-desmoglein-3 autoantibodies. Gynecologic evaluation in patients with pemphigus, including a careful evaluation of Pap smears, should be recommended. (J Am Acad Dermatol 2012;67:409-16.)

Key words: acantholytic cells; atypical squamous cells of undetermined significance; genital involvement; Papanicolaou smears; pemphigus foliaceus; pemphigus vulgaris.

Pemphigus is a rare autoimmune blistering disease of the skin and mucous membranes with a yearly incidence of 0.75 to 5 cases per million.[1] It is characterized by intraepidermal blisters caused by acantholysis as a result of IgG autoantibodies against desmosomes, the major adhesion structures of epidermal keratinocytes. Its main forms are pemphigus vulgaris (PV) and pemphigus foliaceus (PF).[1]

Patients with PF present with cutaneous lesions whereas patients with PV may also show mucous membrane involvement. Skin lesions in PV include vesicles, blisters, erosions, and crusts with variable severity and extension. Most patients with PV have

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mucous membrane erosions and, although oral mucosa is the most common affected site, lesions have been described on other mucous membrane sites including the pharynx, larynx, esophagus, conjunctiva, and genital tract.[1-4] Epidermal cleavage in PF occurs within the superficial layers, whereas blisters in PV are usually at the suprabasilar level.

The frequency of female vulvo-cervico-vaginal involvement in PV is scarcely reported[2,5,6] and so far there is no evidence of genital finding in PF.

The occurrence of PV lesions involving the uterine cervix is clinically relevant as it may be misdiagnosed as a malignant condition when acantholytic cells are detected in cervical smears.[1-3] Valente et al[7] described a patient with PV without clinically active lesions who underwent an unnecessary hysterectomy because of atypical Papanicolaou (Pap) smear findings that persisted even after surgery. She was later given a diagnosis of PV after histopathological reevaluation.

The objective of this study is to analyze the involvement of the female genital tract in both patients with PV and PF.

We examined 41 patients with PV and 15 with PF who submitted to gynecologic examination and Pap smears. We also evaluated the clinical and serologic status of pemphigus correlating with gynecologic findings of each patient.

CAPSULE SUMMARY

- Genital involvement in patients with pemphigus vulgaris has been rarely reported. It has not been reported in patients with pemphigus foliaceus (PF).
- The study emphasizes genital lesions in female patients with PF, and shows that disease reactivation in pemphigus vulgaris and PF may target genital sites. Moreover, this study demonstrates the clinical relevance of Papanicolaou smears in pemphigus vulgaris and PF.
- This study emphasizes the relevance of gynecologic evaluation and careful analysis of Papanicolaou smears of patients with pemphigus.

METHODS

The study was carried out at the Autoimmune Blistering Disease Clinic, Department of Dermatology, University of São Paulo Medical School, Brazil, and was approved by the local ethics committee.

In all, 56 female patients given a diagnosis of PV (41) or PF (15) were evaluated from May 2009 to February 2010. The diagnosis of pemphigus was based on the presence of clinical features of the disease, histopathological examination with hematoxylin-eosin stain, direct immunofluorescence, indirect immunofluorescence (IIF), and enzyme-linked immunosorbent assay (ELISA).

IIF using human foreskin as substrate was performed on serum: 4-μm cryostat-cut sections of human foreskin were incubated with sera dilutions starting at 1:20 for 60 minutes. The slides were then washed in Tris-buffered saline twice (20 minutes each) and then covered with fluorescein isothiocyanate-conjugated goat antihuman IgG, 1:30 (Sigma, St. Louis, MO), for 30 minutes. After two additional 20-minute washes (Tris-buffered saline), the slides were mounted in buffered glycerol and examined under an epiluminescent microscope (Zeiss, Goettingen, Germany).

ELISA was performed on serum as well: sera samples (1:100 dilution) were added to microwells coated with baculovirus-expressed desmogleins (Dsg) for 60 minutes. After washing, horseradish peroxidase-conjugated IgG was added and incubated for 60 minutes. After another washing, the peroxidase substrate was added and allowed to incubate for an additional 30 minutes. Then, 1.0N sulfuric acid solution was added to each well to terminate the enzyme reaction and to stabilize the color development. The absorbance was measured at 450 nm by an ELISA reader (MBL, Nagoya, Japan). The index was calculated as follows: index = (optical density [OD] of tested serum − OD of negative control)/(OD of positive control serum − OD of negative control) × 100. The interpretation of results was made according to the following:

Dsg-1:

- less than 14 = negative;
- 14 to 20 = indeterminate;
- greater than 20 = positive.

Dsg-3:

- less than 9 = negative;
- 9 to 20 = indeterminate;
- greater than 20 = positive.

Each patient also underwent a detailed review of their clinical history. The following information was collected: diagnosis; age; onset of disease; symptoms of genital disease; presence of vulvar, vaginal, and/or cervical involvement; other affected anatomic sites (skin and other mucous membranes); treatment; and disease activity.

Abbreviations used:

ASC-US: atypical squamous cells of undetermined significance
Dsg: desmoglein
ELISA: enzyme-linked immunosorbent assay
HSIL: high-grade squamous intraepithelial lesion
IIF: indirect immunofluorescence
LSIL: low-grade squamous intraepithelial lesion
OD: optical density
Pap: Papanicolaou
PF: pemphigus foliaceus
PV: pemphigus vulgaris

Patients were classified according to the following clinical criteria adapted from the consensus statement on definitions of disease, end points, and therapeutic response for pemphigus[8]:

1. Baseline: the day that therapy is started by a physician;
2. Complete remission:
   a. Complete remission off therapy (absence of new or established lesions while the patient is off all systemic therapy for at least 2 months);
   b. Complete remission on therapy (absence of new or established lesions while the patient is receiving prednisone [or the equivalent] at 10 mg/d for at least 2 months);
3. Partial remission:
   a. Partial remission on therapy (presence of transient new lesions that heal within 1 week while patient is receiving systemic therapy);
   b. Partial remission on minimal therapy (presence of transient new lesions that heal within 1 week while patient is receiving prednisone <10 mg/d and/or minimal adjuvant therapy and/or topical treatment);
4. Relapse/flare (appearance of lesions that do not heal spontaneously within 1 week or by extension of established lesions, in a patient who has achieved disease control).

All 41 patients with PV and 15 with PF were also examined by a gynecologist and were screened with Pap smears.

Cervical and vaginal smears were taken separately with Ayre spatulas, spray-fixed with commercial fixative, stained with the routine Pap stain, and reported by a cytopathologist who was not aware of the patient's history and clinical status.

Table I. Distribution of mucous sites in mucous and mucocutaneous pemphigus vulgaris

Sites of involvement	Mucous (n = 16)	Mucocutaneous (n = 15)
Vulva	1	6
Vagina	0	0
Uterine cervix	1	1
Oral	15	12
Pharynx	1	0
Larynx	3	0
Esophagus	1	2
Conjunctiva	0	1

In this study, Pap smear results were reported according to the 2001 Bethesda system[9]:

1. Negative for intraepithelial lesion or malignancy, which includes normal, reactive cellular changes associated with inflammation (includes typical repair) and atrophy;
2. Squamous cell abnormalities:
   a. Atypical squamous cells of undetermined significance (ASC-US);
   b. Atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion (HSIL);
   c. Low-grade squamous intraepithelial lesion (LSIL);
   d. HSIL;
   e. Squamous cell carcinoma;
3. Glandular epithelial cell abnormalities.

Patients given a diagnosis of ASC-US, atypical squamous cells that cannot exclude HSIL, LSIL, or HSIL by Pap smear were referred to colposcopy. Lesions found in colposcopy were biopsied and histopathological analysis was performed.

RESULTS

Demographic and clinical findings

In all, 41 patients had PV and 15 patients had PF. In the PV group, age at the evaluation varied from 24 to 72 years (mean ± SD, 45 ± 12 years). In the PF group, age at the evaluation varied from 24 to 69 years (mean ± SD, 49 ± 11 years).

Of 41 patients with PV, 31 had active disease: 15 with mucocutaneous PV and 16 with mucous membrane only involvement. Ten patients with PV had no active lesions. Distribution of mucous membrane sites in PV is seen in Table I.

Genital involvement was observed in 9 of 41 patients with PV (22%) (Table II), although genital symptoms were reported in 19 of 41 patients (46%).

Table II. Clinical and laboratory evaluation of 9 patients with pemphigus vulgaris and genital involvement

Patient No.	Site of genital involvement	Genital symptoms	Other mucosal sites of involvement		Pap smears	Clinical status*	IIF (IgG)	ELISA	
			MCPV	MPV				Anti-Dsg-3	Anti-Dsg-1
5	Lmi, V	Dyspareunia		O, L, E	ASC-US	4	1:160	+	+
8	Lmi, V	—	O		Normal	4	1:1280	+	+
10	Lma, Lmi	Pruritus	O, E, C		Inflammatory	4	—	+	+
11	Lma	Pruritus	O		Inflammatory	1	1:2560	+	+
12	Uterine cervix	—			ASC-US	2a	—	—	Indeterminate
20	Lma, Lmi	Pruritus	O, E		Normal	1	1:320	+	+
31	Lma, Lmi	Pruritus	O		Inflammatory	1	NP	+	+
34	Uterine cervix	—	O		ASC-US	4	1:1280	+	+
39	Lma, Lmi, V	Pruritus and vaginal discharge	O		Inflammatory	4	1:640	+	+

ASC-US, Atypical squamous cells of undetermined significance; *C*, conjunctiva; *Dsg*, desmoglein; *E*, esophagus; *ELISA*, enzyme-linked immunosorbent assay; *IIF*, indirect immunofluorescence; *L*, larynx; *Lma*, labia majora; *Lmi*, labia minora; *MCPV*, mucocutaneous pemphigus vulgaris; *MPV*, mucous pemphigus vulgaris; *NP*, not performed; *O*, oral cavity; *Pap*, Papanicolaou; *V*, vestibule.
*1 = Baseline; 2a = complete remission off therapy; 4 = relapse.

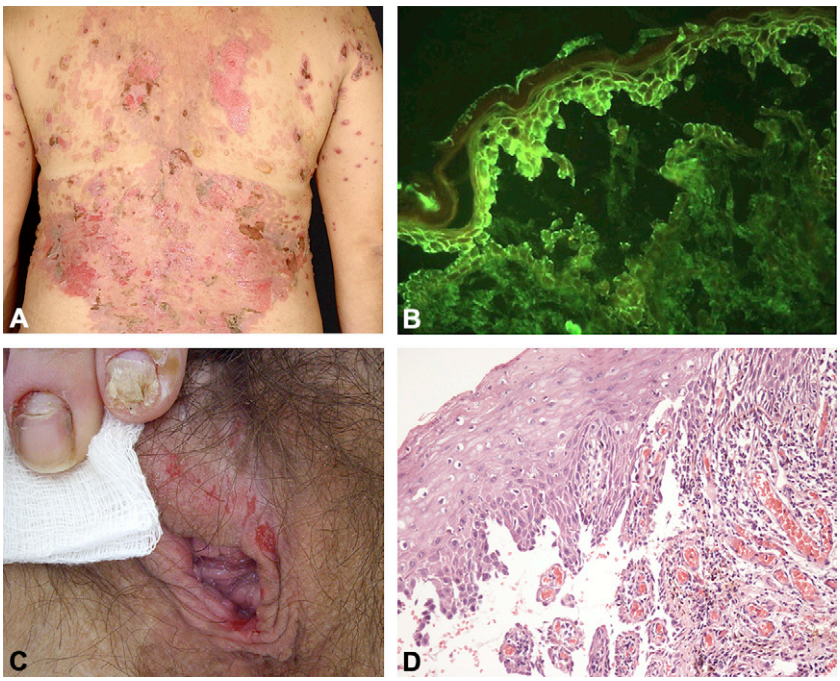

Fig 1. Pemphigus vulgaris. **A**, Multiple erosions and bullae. **B**, Intraepithelial intercellular IgG staining. **C**, Erosions on vulva and paronychia. **D**, Vulvar histopathology revealing suprabasilar cleavage with acantholysis. (**B** and **D**, Original magnifications: **B**, ×400; **D**, ×200.)

Eight of 9 patients with genital lesions were in baseline or major recurrent disease and 5 of 41 patients without genital lesions were in baseline or major recurrent disease. Erosions were the main genital finding in PV (Fig 1). The most affected vulvae site was the labia minora (6 of 9 patients or 67%).

Twelve of 15 patients with PF had active disease. Genital involvement was observed in 4 of 15 patients with PF (27%) (Table III), although genital symptoms were reported in 8 of 15 patients (53%). One patient with genital lesion was in major recurrent disease and 3 of 11 patients without genital lesions were in baseline or major recurrent disease. Erosions were the only genital finding in PF (Fig 2). Two of 4 had labia minora involvement (50%) and two of 4 had labia majora involvement (50%).

Table III. Clinical and laboratory evaluation of 4 patients with pemphigus foliaceus and genital involvement

Patient No.	Site of genital involvement	Genital symptoms	Pap smears	Clinical status*	IIF (IgG)	ELISA	
						Anti-Dsg-3	Anti-Dsg-1
44	Lma	—	Inflammatory	3a	1:160	—	+
49	Lmi	Pruritus	Inflammatory	3b	NP	—	+
55	Lma	—	Inflammatory	3b	1:160	—	+
56	Lmi	Pruritus	Inflammatory	4	—	Indeterminate	+

Dsg, Desmoglein; *ELISA*, enzyme-linked immunosorbent assay; *IIF*, indirect immunofluorescence; *Lma*, labia majora; *Lmi*, labia minora; *NP*, not performed; *Pap*, Papanicolaou.
*3a = Partial remission on therapy; 3b = partial remission on minimal therapy; 4 = relapse.

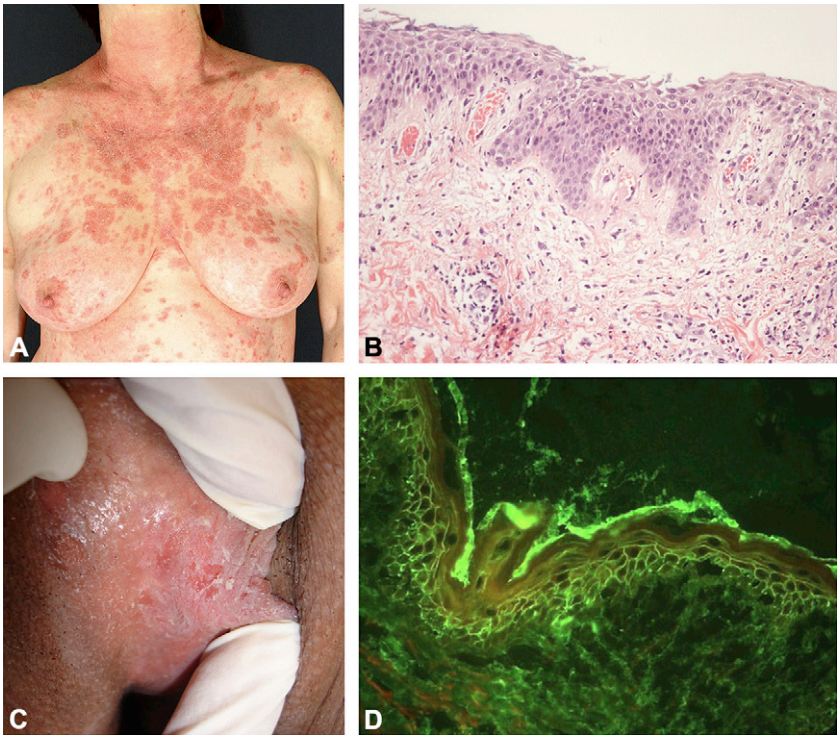

Fig 2. Pemphigus foliaceus. **A**, Erosions. **B**, Skin histopathology revealing subcorneal acantholysis. **C**, Erosion on vulva. **D**, Intraepidermal intercellular IgG deposits. (**B** and **D**, Original magnifications: **B**, ×200; **D**, ×400.)

Pap smears

Pap smears were collected from 41 patients with PV and 15 with PF and were analyzed by a cytopathologist who was not aware of the clinical status of these patients.

Pap smears were read as normal in 8 of 41 patients with PV, inflammatory in 27, ASC-US in 5, and LSIL in one. In the 5 patients with PV and cytologic ASC-US, two had mucous PV: one had vulvar (labia minora and vestibule erosions), oral, esophageal, and laryngeal lesions, and one had only uterine cervix lesions (Fig 3). Three patients with cytologic ASC-US had mucocutaneous PV: one had oral, pharyngeal, and laryngeal lesions; one had only oral lesions; and one had oral and cervical lesions.

Three of 5 patients with PV and cytologic ASC-US were in relapse, one was at baseline, and one was in complete remission off therapy. The patient with PV and cytologic LSIL was in complete remission off therapy.

In the 15 patients with PF, Pap smears were read as normal in 3, inflammatory in 11, and ASC-US in one. The patient with ASC-US-positive PF was in complete remission off therapy (Fig 4). Table IV shows the patients with pemphigus (5 PV and 1 PF) and cytologic ASC-US in Pap smears.

The ASC-US or LSIL Pap smears were then reviewed by a dermatopathologist. Acantholytic cells were detected in those patients with a previous ASC-US result. The review of the patient with

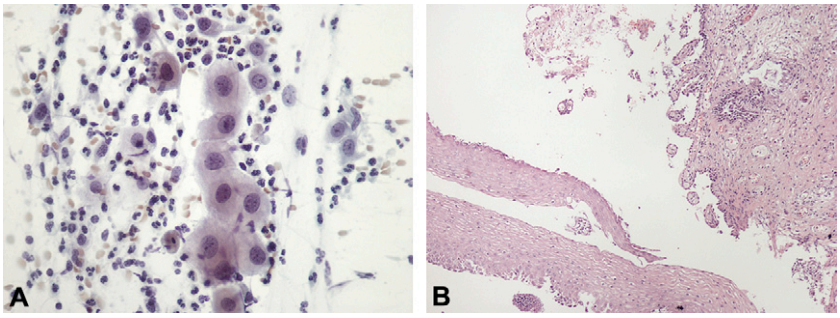

Fig 3. Pemphigus vulgaris. **A**, Papanicolaou smear showing acantholytic cells. **B**, Uterine cervix histopathology revealing suprabasilar cleavage with acantholysis. (**A** and **B**, Original magnifications: **A**, ×400; **B**, ×100.)

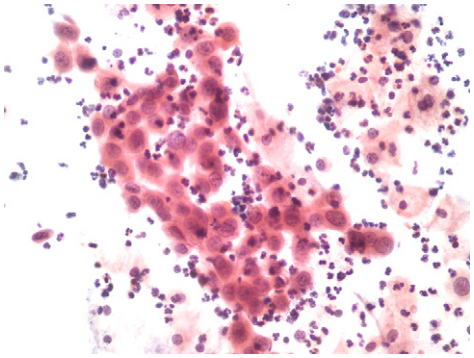

Fig 4. Pemphigus foliaceus. Papanicolaou smear showing acantholytic cells in patient with pemphigus foliaceus. (Original magnification: ×400.)

PV and the LSIL result revealed no acantholytic cells.

All 6 patients with cytologic ASC-US and one patient with cytologic LSIL were referred to colposcopy. Two of them had uterine cervix erosions and were submitted to cervical biopsy specimen that revealed acantholytic suprabasilar bullae.

Laboratory findings

IIF analysis was positive in 9 patients of the PF group, with titers ranging from 1:40 to 1:2560 (mean titer 1:640). IIF was also positive in 22 patients of the PV group, with titers ranging from 1:80 to 1:2560 (mean titer 1:640).

Autoantibodies against recombinant Dsg-1 and Dsg-3 were detected by ELISA (MBL). Of the 41 patients with PV ELISA anti-Dsg-3 was positive in 32 patients, negative in 6 patients, indeterminate in two patients, and not performed in one patient. Anti-Dsg-1 was positive in 17 of 40 patients with PV. Of the 15 patients with PF, ELISA anti-Dsg-1 was positive in 11 patients, negative in one patient, indeterminate in one patient, and not performed in two patients. None of the patients with PF who were tested for anti-Dsg-3 via ELISA had positive findings.

Treatment

Patients with PV were treated with prednisone (1 mg/kg/d with gradual reduction) and other immunosuppressants (mycophenolate mofetil, 35-45 mg/kg/d; azathioprine, 2 mg/kg/d; and cyclophosphamide, 2 mg/kg/d). Therapy for PF included prednisone (1 mg/kg/d with gradual reduction), triamcinolone, and dapsone.

DISCUSSION

PV is characterized by vesiculobullous lesions involving the oral mucosa, skin, and, less frequently, other mucosal surfaces such as the esophagus, conjunctiva, nasal mucosa, pharynx, larynx, genital tract, and anal mucosa.[1,3] In the majority of patients with PV, the oral cavity is the first site of the disease, whereas in others it is often involved at some point during the clinical course.

PV is known to affect the female genital tract, despite scarce reports in the literature. In the current study, genital involvement was observed in 9 of 41 patients with PV (22%); vulva was the major genital site of involvement (17%), followed by the uterine cervix (5%). No vaginal lesions were seen. Overall, in our patients with PV, the oral mucosa was the most common site of mucous membrane involvement, followed by vulvar involvement.

Akhyani et al[2] studied 77 patients with PV (mean age 44.7 years) and new-onset or major recurrence disease, and found 39 patients (51%) with genital disease (vulva, cervix, and vagina). In their series, 51% of patients had vulvar, 18% had vaginal, and 8% had cervical involvement. Malik and Ahmed[6] reported 34 cases with genital involvement (mean age 49 years) and found that 34% of their patients had recurrent disease and all of their patients had involvement of multiple sites, especially of the oral mucosa.

It is relevant to emphasize that we detected a lower percentage of genital involvement compared

Table IV. Clinical and laboratory evaluation in 6 patients with pemphigus and positive atypical squamous cells of undetermined significance result in Papanicolaou smears

Patient No.	Diagnosis	Site of genital involvement	Genital symptoms	Others mucosal sites of involvement		Pap smears	Clinical status*	IIF (IgG)	ELISA	
				MCPV	MPV				Anti-Dsg-3	Anti-Dsg-1
5	PV	Vulva	Dyspareunia		O, L, E	ASC-US	4	1:160	+	+
12	PV	Uterine cervix	–			ASC-US	2a	–	Indeterminate	–
21	PV	–	Discharge	O		ASC-US	1	1:160	+	+
24	PV	–	–	O, P, L		ASC-US	4	NP	+	–
34	PV	Uterine cervix	–	O		ASC-US	4	1:1280	+	+
48	PF	–	–	NA	NA	ASC-US	2a	NP	–	–

ASC-US, Atypical squamous cells of undetermined significance; *Dsg*, desmoglein; *E*, esophagus; *ELISA*, enzyme-linked immunosorbent assay; *IIF*, indirect immunofluorescence; *L*, larynx; *MCPV*, mucocutaneous pemphigus vulgaris; *MPV*, mucous pemphigus vulgaris; *NA*, not applicable; *NP*, not performed; *O*, oral cavity; *P*, pharynx; *Pap*, Papanicolaou; *PF*, pemphigus foliaceus; *PV*, pemphigus vulgaris.
*1 = Baseline; 2a = complete remission off therapy; 4 = relapse.

with the results of Akhyani et al.[2] This may be because of a different approach in patients' evaluation, which included diverse clinical stages of disease. However, when considering the 9 patients with genital lesions in our study, 5 were in relapse and 3 were at baseline, similar to the patients reported by Akhyani et al.[2]

In this study it seems that genital lesions were more frequent in patients with active disease (baseline or recurrence). A long-term follow-up and inclusion of more patients should be performed.

Genital manifestations in PV may be the sole manifestations of the disease, which emphasizes the importance of genital evaluation. One of 51 patients with PV from our group had exclusive uterine cervix erosions, without detectable circulating autoantibodies. Occasional reports of uterine cervix or vaginal lesions have been described.[5,10,11] Zosmer et al[12] reported in a 56-year-old woman active uterine cervical lesions of PV even with control of cutaneous lesions, and emphasized the need for vaginal examination. Gupta el al[10] described a case of PV diagnosed from cervical lesions, and Batta et al[5] showed a patient with PV who only presented vaginal wall erosions. Valente et al[7] and Friedman et al[13] reported refractory PV in the uterine cervix and reinforced the necessity of careful genital examination.

In patients with PF the lesions are traditionally restricted to the skin without previous reports of female genital tract involvement. In the current report, genital lesions were observed in 4 of 15 patients with PF (27%) and the vulva was the only affected site. One of our patients with PF, in partial remission on minimal therapy, presented exclusively with symptomatic vulvar erosions and had detectable anti-Dsg-1 antibodies by ELISA.

Acantholytic cells found in Pap smears of patients with pemphigus and uterine cervix involvement have been known to be misinterpreted as an indication of cervical dysplasia in Pap smears.[3,7,10,11,14-17]

Abnormal Pap smear results (ASC-US) are not necessarily a diagnostic finding of squamous intraepithelial neoplasia, but a close gynecologic follow-up is essential.[18]

In 6 of 56 patients with pemphigus (5 PV and 1 PF), initial Pap smear findings were classified as ASC-US. These results were reviewed by a second pathologist, who concluded that the abnormalities were compatible with acantholytic cells rather than ASC-US. The 6 patients underwent colposcopy, which revealed cervical erosions in two individuals with PV. Histopathologic evaluation of these two cases confirmed acantholysis.

Interestingly, the single patient with PF and acantholytic cells at Pap smear was considered to

be in complete remission off therapy, without genital lesions, and without circulating anti-Dsg-1 and Dsg-3 autoantibodies. Possible explanations for this finding are either epitope spreading (shift from PF to PV in progression) or ultrastructural changes in the uterine cervix preceding acantholysis.[19]

Relevant findings of this study include: vulvar lesions were the second most frequent site of PV mucosal involvement; symptomatic genital involvement (especially vulvar) may be a PF clinical presentation; gynecologic evaluation of patients with pemphigus should be performed; and a careful evaluation of Pap smears in patients with pemphigus is needed to avoid misdiagnosis and potentially drastic clinical consequences (eg, hysterectomy).

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