

## LETTERS TO THE EDITOR

### Pemphigus Vulgaris of the Uterine Cervix: Misinterpretation of Papanicolaou Smears

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Accepted March 20, 2006.

Sir,

Mucosal involvement is a common finding in pemphigus vulgaris (PV), especially oral lesions, which precede skin blisters in up to 70% of cases (1). Less frequently, other epithelial tissues that also express desmoglein 3 may be affected, for example, pharynx, larynx, nasal cavity, conjunctiva, anus, penis, urethra, vagina, vulva and oesophagus. The occurrence of PV lesions involving the cervix uteri has rarely been reported in the literature. The relevance of the involvement of this site lies in the fact that acantholytic cells in routine cervical smears may lead to false positive diagnoses of cervical neoplasia.

#### CASE REPORT

A 22-year-old woman first presented to our dermatological department with painful, rounded ulcerations on the oral mucosa, desquamative gingivitis and absence of cutaneous lesions. She had been diagnosed previously and treated for PV five years earlier in another institution, and the patient related that cutaneous lesions were present at that time.

Histological examination of the oral mucosa biopsy showed a suprabasal cleavage with acantholysis. Direct immunofluorescence revealed deposition of IgG and C3 in the intercellular spaces of the epithelium. Indirect immunofluorescence analysis using normal human foreskin sections as substrate exhibited intraepithelial IgG auto-antibodies at a 1:5120 titre. Auto-antibodies against recombinant desmogleins (dsg) 1 and 3 were detected by enzyme-linked immunosorbent assay (ELISA, MBL, Japan). The patient's serum was strongly positive for anti-dsg 3 (index value: 226; cut-off: 20) and weakly positive for anti-dsg 1 (index value: 28; cut-off: 20).

After 2 years of follow-up, she experienced a period of exacerbation of her disease: her oral lesions got worse and a vegetating plaque appeared on the right axilla, which was biopsied and revealed a suprabasal acantholysis. Surprisingly, after a routine gynaecologist consultation, the patient was informed that her Papanicolaou smear was suggestive of cervical cancer. She had no gynaecological symptoms, such as dyspareunia, vaginal bleeding or discharge. The patient was then referred to our gynaecological department and, on colposcopic examination, multiple erosions and a positive Nikolsky sign were noticed on the cervix (Fig.

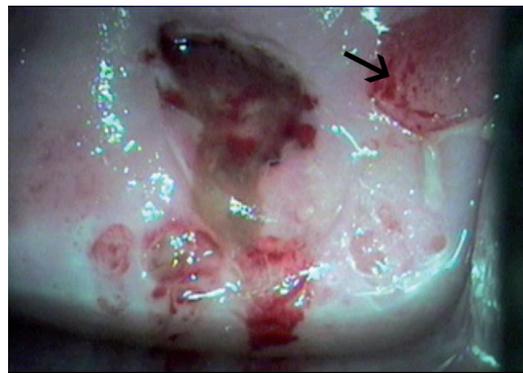


Fig. 1. Multiple erosions on the cervix and the positive Nikolsky sign (arrow).

1). The Papanicolaou specimen revealed acantholytic cells (Fig. 2A). Histopathology was consistent with PV and revealed no signs of malignancy (Fig. 2B). Direct immunofluorescence showed intercellular deposits of IgG and C3 on the cervical epithelium (Fig. 2c).

Treatment with 3.5 mg/kg/day of mycophenolate mofetil and 0.3 mg/kg/day of prednisone induced considerable improvement. Her cervical and axillae lesions entered complete clinical remission. The oral lesions also showed significant improvement, but the desquamative gingivitis persists.

#### DISCUSSION

PV-involvement of the uterine cervix has seldom been reported, with fewer than 20 cases described in the literature (2–14). Since dermatologists do not usually perform routine gynaecological examinations, the involvement of this site may be more frequent than suggested by the rare reports. In most of the published cases, cervical involvement was suspected because patients had a prior diagnosis of PV and gynaecological symptoms, such as vaginal discharge, spotting, bleeding after intercourse or dyspareunia. However, some patients were asymptomatic or even presented cervix involvement as the first sign of their disease (5, 8, 10, 13). In a series of 14 patients with PV, 11 showed a positive Nikolsky sign after the application of pressure to the cervical surface with a cotton-tipped applicator, suggesting that cervix involvement, although silent, is frequent during the active stage of pemphigus (15).

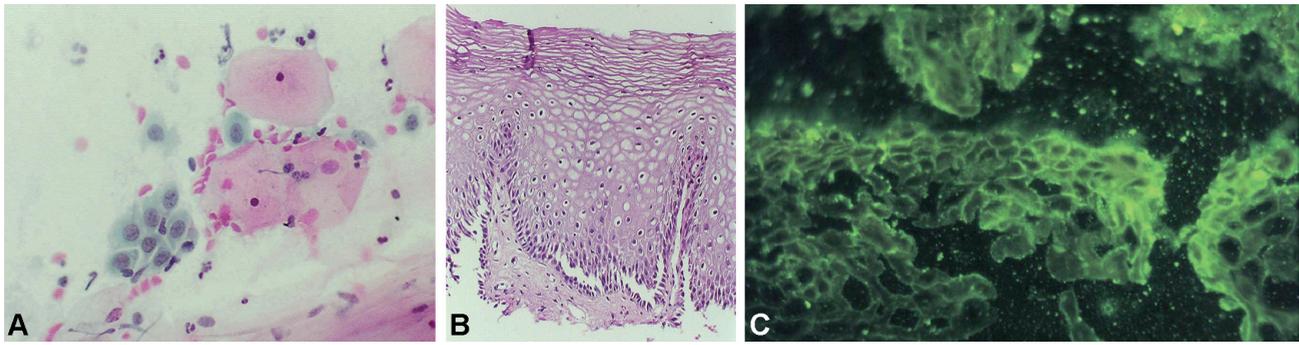


Fig. 2. (A) Cervical smear showing acantholytic cells (Papanicolaou stain). (B) Cervical biopsy revealing suprabasal cleavage with acantholysis. (C) Direct immunofluorescence showing intercellular deposits of IgG and C3 on the cervical epithelium.

The fact that the Papanicolaou smears of patients with cervical PV typically exhibit acantholytic cells is of practical importance, as they may be misinterpreted by the cytopathologist as a reparative or inflammatory reaction, or even as suggestive of cervical neoplasia, especially when the clinical diagnosis of PV is not known (5). Furthermore, patients may present abnormal Papanicolaou smears even without any obvious cervical or vaginal lesions. Valente et al. (10) described a 43-year-old woman with subclinical PV involving the uterine cervix who was submitted to a total abdominal hysterectomy and bilateral salpingo-oophorectomy owing to persistent atypical Papanicolaou smears. After surgery, smears of the vaginal vault continued to show abnormal cells and re-examination of the surgical material ultimately led to the diagnosis of PV.

Some authors believe that patients with PV have an increased risk of developing a neoplastic process of the cervical epithelium (7, 9). The prolonged use of immunosuppressive agents and recurrent erosions leading to chronic inflammation are the implied causes. Dvoretzky et al. (9) published 2 cases of microinvasive squamous cell carcinoma of the uterine cervix developing in association with uterine cervical pemphigus in patients with histories of long-standing PV. A patient with PV with involvement of the cervix and carcinoma of the endometrium has also been reported (14).

#### ACKNOWLEDGEMENTS

The authors thank biologists Alexandre Marques Périgo and Lígia M.I. Fukumori, Immunodermatopathology Laboratory, Department of Dermatology, University of São Paulo.

#### REFERENCES

- Batta K, Munday PE, Tatnall FM. Pemphigus vulgaris localized to the vagina presenting as chronic vaginal discharge. *Br J Dermatol* 1999; 140: 945–947.
- Cunha PR, Oliveira JR, Salles MJ, Jamora J, Bystryn J. Pemphigus vulgaris with involvement of the cervix treated using thalidomide therapy. *Int J Dermatol* 2004; 43: 682–684.
- Friedman D, Haim S, Paldi E. Refractory involvement of cervix uteri in a case of pemphigus vulgaris. *Am J Obstet Gynecol* 1971; 110: 1023–1024.
- Mikhail GR, Drukker BH, Chow C. Pemphigus vulgaris involving the cervix uteri. *Arch Dermatol* 1967; 95: 496–498.
- Gupta S, Sodhani P, Jain S. Acantholytic cells exfoliated from pemphigus vulgaris of the uterine cervix. *Acta Cytol* 2003; 47: 795–798.
- Chan E, Thakur A, Farid L, Lessin S, Uberti-Benz M, James W. Pemphigus vulgaris of the cervix and upper vaginal vault: a cause of atypical papanicolaou smears. *Arch Dermatol* 1998; 134: 1485–1486.
- Lonsdale RN, Gibbs S. Pemphigus vulgaris with involvement of the cervix. *Br J Dermatol* 1998; 138: 363–365.
- Bourgeois-Droin Ch, Granier F, Pedreiro J, Madinier V, Grossin M. Localisations vulvo-vaginales et du col utérin révélatrices d'un pemphigus vulgaire efficacité des sels d'or. *Ann Dermatol Venereol* 1990; 117: 894–895.
- Dvoretzky PM, Bonfiglio TA, Patten SF Jr, Helmkamp BF. Pemphigus vulgaris and microinvasive squamous-cell carcinoma of the uterine cervix. *Acta Cytol* 1985; 29: 403–410.
- Valente PT, Ernst CS, Atkinson BF. Pemphigus vulgaris with subclinical involvement of the uterine cervix – report of a case with persistence of abnormal Papanicolaou smears posthysterectomy. *Acta Cytol* 1984; 28: 681–683.
- Zosmer A, Kogan S, Frumkin A, Dgani R, Lifschitz-Mercer B. Unsuspected involvement of the female genitalia in pemphigus vulgaris. *Eur J Obstet Gynecol Reprod Biol* 1992; 47: 260–263.
- Kaufman RH, Watts JM, Gardner HL. Pemphigus vulgaris: genital involvement. *Obstet Gynecol* 1969; 33: 264–266.
- Wright C, Pipingas A, Grayson W, Leiman G. Pemphigus vulgaris of the uterine cervix revisited: case report and review of the literature. *Diagn Cytopathol* 2000; 22: 304–307.
- Krain LS, Rosenthal L, Newcomer VD. Pemphigus vulgaris involving the cervix associated with endometrial carcinoma of the uterus: a case report with immunofluorescent findings. *Int J Dermatol* 1973; 12: 220–228.
- Sagher F, Bercovici B, Romem R. Nikolsky sign on cervix uteri in pemphigus. *Br J Dermatol* 1974; 90: 407–411.