

CASE REPORT

Villoglandular adenocarcinoma of cervix – a tumour with bland cytological features: report of a case missed on cytology

Gita JAYARAM, MDPATH, FRCPath and Abdul RAZAK AR, DipMLT

Department of Pathology, University Malaya Medical Centre, Kuala Lumpur

Abstract

The diagnosis of villoglandular adenocarcinoma of cervix on cytological smears is often missed due to the relatively bland cytological features of this tumour. A 45-year-old female with an exophytic cervical growth had three cervical smears reported as unsatisfactory. A cervical biopsy followed by Wertheim's hysterectomy showed a villoglandular adenocarcinoma (VGA) of cervix. Vaginal recurrence of VGA was again missed on the first post-operative vault smear. The second and third vault smears showed characteristic features of VGA that enabled correct identification. Review of some of the smears previously reported as unsatisfactory showed architectural features of VGA in the three dimensional (3-D) fragments that were previously considered to be benign.

Keywords: Cytology, villoglandular carcinoma, uterine cervix, neoplasm, papillary.

INTRODUCTION

Well-differentiated villoglandular adenocarcinoma (VGA) is a recently described subtype of cervical adenocarcinoma that is reported to occur predominantly in young women with distinct clinicopathological features and an excellent prognosis.¹⁻⁵ Cytological features of VGA have been described in very few publications and most of these are retrospective analyses.^{3,6-8} The tumour cells of VGA are relatively bland in appearance and are difficult to distinguish from reactive glandular cells in cervical smears. Therefore the majority of VGAs are missed on screening cytology. This report describes one such case.

CASE REPORT

A 45-year-old Chinese female presented in July 2000 to the gynaecological clinic of the University Malaya Medical Centre with an exophytic cervical growth. A cervical smear and cervical biopsy were done. The smear was reported as "unsatisfactory due to scanty cellularity" while the cervical biopsy was reported as an adenocarcinoma. In August 2000, a repeat cervical smear was reported as unsatisfactory (this time due to thick smear). In October 2000 the patient had a Wertheim's hysterectomy and adjuvant chemotherapy. A histological report of

VGA of cervix was given. Surgical margins and lymph nodes were uninvolved by tumour. A vault smear done in December 2000 was reported as unsatisfactory due to scanty cellularity. In March 2001 an erythematous lesion in the vault was biopsied and reported as recurrent VGA. Following vault irradiation, a vault smear was repeated in September 2001; this was reported as within normal limits. Vault smear done in November and December 2001 were reported as suggestive of recurrent VGA.

Cytological features

Detailed cytomorphological review of all the cervical and vault smears showed the following: (1) The July 2000 smear showing scanty cellularity correctly labeled as unsatisfactory. (2) The August 2000 smear (that was labeled as "unsatisfactory due to thick smear") showed fragments of glandular cells of endocervical type in which the morphology of individual cells could not be ascertained due to the thickness of the fragments (Fig. 1A). These fragments however did show papillo-glandular configurations with smooth borders. (3) The vault smear of December 2000 was scanty but occasional three-dimensional (3-D) clusters of cells similar in appearance to the clusters seen in the cervical smear of August 2000 were present. (4) The vault smear of September 2001

(considered to be “within normal limits”) showed 3-D clusters and occasional monolayered sheets of cells that showed bland nuclear features (Fig. 1B). These had presumably been considered to represent vaginal adenosis. (5) The two vault smears done in November and December 2001 showed numerous 3-D clusters with villoglandular configurations composed of small cells that showed high N:C ratios with mild nuclear hyperchromasia and granular chromatin (Fig. 2). There was marked cellular overlapping. Palisading and columnar appearance were visible at the edges of the clusters (Fig. 2). Nucleoli were inconspicuous although occasional cells showed micronucleoli.

Histological features

Histological sections from the cervical biopsy, the Wertheim’s hysterectomy specimen and the recurrent vaginal tumour showed similar appearances. The tumour was exophytic and showed a well-differentiated villoglandular papillary pattern with long slender papillae populated by tall columnar cells with basal nuclei (Figs. 3 & 4). Nuclear atypia and mitotic activity were relatively inconspicuous.

DISCUSSION

The malignant cells of VGA are difficult to distinguish from reactive glandular cells. VGAs of cervix are distinguished by three main histological features: exophytic proliferation, papillary architecture and mild or moderate cellular atypicity.⁹ Most of the cases reported have involved younger patients (25-45 years of age) than in the usual type of cervical adenocarcinoma.⁹ Stromal invasion is usually superficial⁹ and the prognosis is favourable, enabling a conservative surgical approach in at least some of the cases.³ Presence of lymphatic invasion and deep stromal involvement were probably the risk factors for lymph node metastases that were seen in a few cases necessitating adjuvant radiation therapy.¹ Occasionally VGA may be associated with squamous cell carcinoma^{2,9} or with moderately differentiated papillary adenocarcinoma.² In such cases the management would be based on the more ominous component.² A single case of VGA of cervix that was demonstrated to be positive for human papilloma virus type 18 by polymerase chain reaction has been reported.¹⁰

Cytological diagnosis of VGA may pose difficulties because it shares morphological

similarities with adenocarcinoma-in-situ, squamous cell carcinoma-in-situ involving endocervical glands, endometrial cells directly sampled with cytobrush and reactive endocervical cells.⁸ Most VGAs are either missed on routine screening or reported as atypical glandular cells of uncertain significance (AGUS).⁷ Cytological descriptions of VGA are usually from retrospective studies. Architecturally long, slender papillae and cohesive branching of epithelial sheets with smooth borders are observed.⁶⁻⁷ Crowding and overlapping of nuclei are prominent features but feathering is unusual.⁶⁻⁷ Nuclei are uniform, small, round or oval with evenly distributed granular chromatin. Nucleoli and mitoses are absent or inconspicuous. Rosettes or strips with peripheral nuclear palisading and pseudostratification may be present.⁸ In the present case, an exophytic tumour was seen on initial presentation; however the cervical smears were either scanty (first smear) or too thick (second smear) with 3-D fragments in which cell morphology could not be well appreciated. On review however it is felt that the architectural pattern of the fragments and the presence of mainly glandular cells in the cervical smear should have led to a suspicion of a glandular neoplasm. Vault smears on the other hand generally show sparse cellularity and the presence of bland looking glandular cells usually leads to an impression of vaginal adenosis, as occurred in the second vault smear in this case. While the first vault smear was scanty, the second one did show 3-D fragments with villoglandular configurations that are not seen in vaginal adenosis and should have been considered to be abnormal. The third and fourth vault smears that were evenly spread showed subtle but unmistakable cytomorphological features of the tumour such as high N:C ratio, granular chromatin, micronucleoli, cell overlapping, columnar appearance and palisading.

Knowledge of the cytomorphology of uncommon variants of cervical carcinoma such as VGA would help greatly in avoiding underdiagnosis as occurred in this case and this indeed is the focus of this case report. From a technical point of view, preparation of thin or evenly spread smears or if possible, liquid cytology preparations would greatly enhance accurate cytomorphological evaluation and diagnosis.

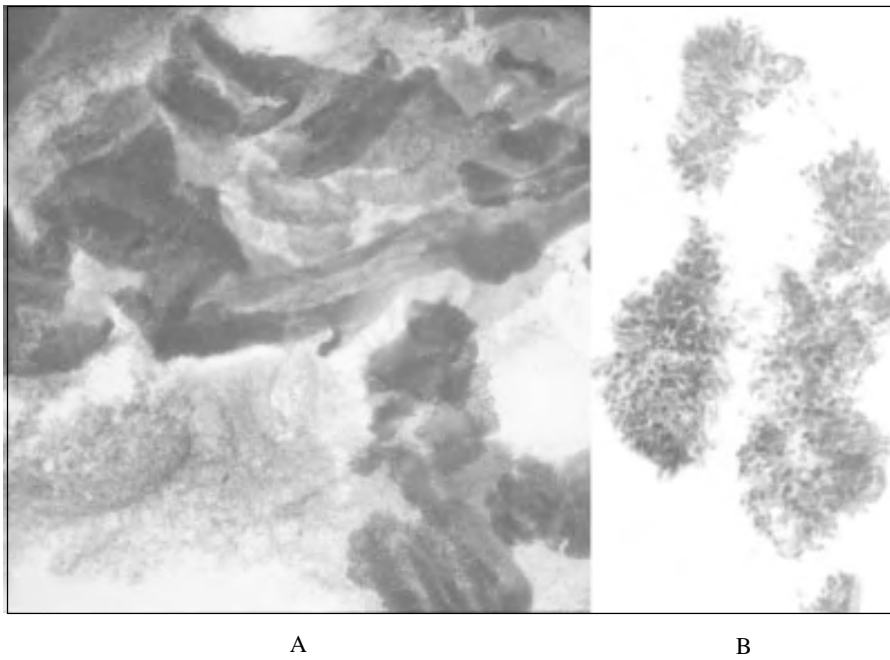


FIG. 1: (A) 3-D fragments of glandular cells in cervical smear. Pap x 80. (B) Monolayered sheets of cells with bland nuclear features in the first post-operative vault smear. Pap x 200.

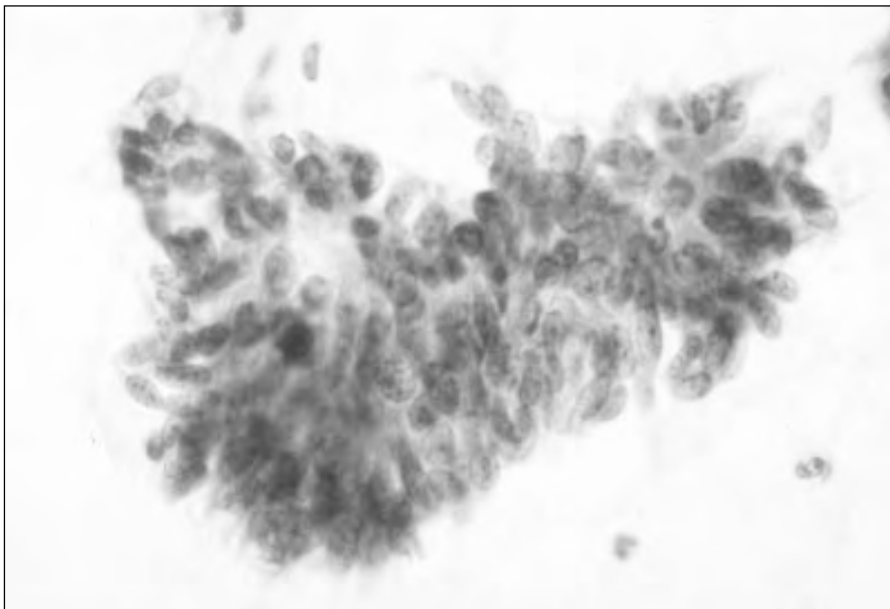


FIG. 2: Cluster of glandular cells with columnar appearance, nuclear crowding and overlapping, granular chromatin and micronucleoli. Pap x 800.

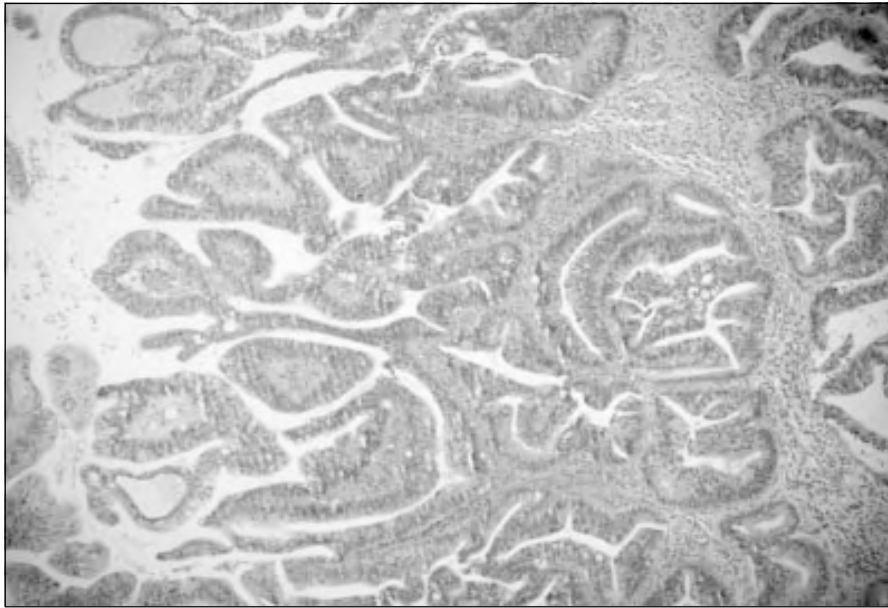


FIG. 3: VGA showing superficial stromal invasion. H&E x 80.

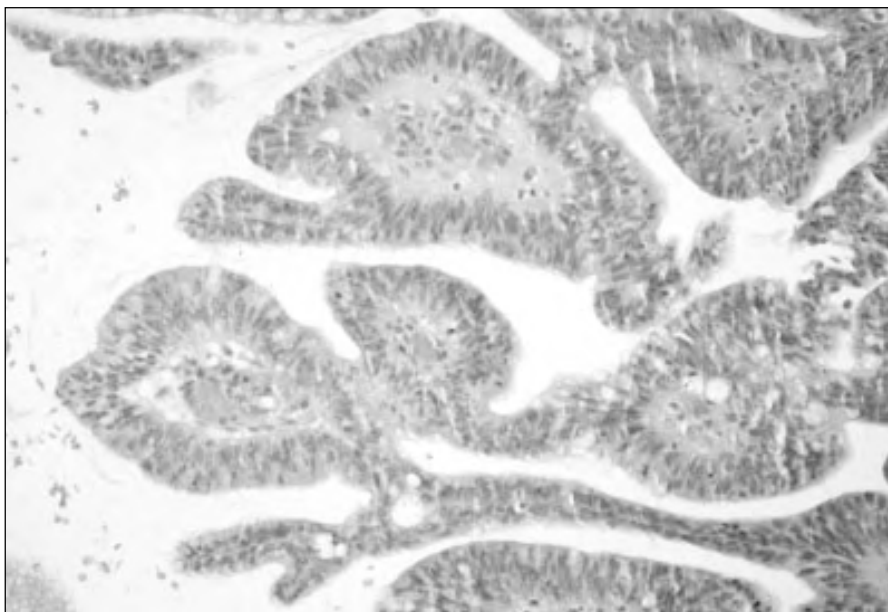


FIG. 4: Section of tumour showing villous processes lined by tall columnar cells with bland nuclear features. H&E x 200.

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