Cytology and its importance for the detection of villoglandular adenocarcinoma

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ABSTRACT

The endocervical villoglandular adenocarcinoma is a rare type of cervical adenocarcinoma that affects mainly young and in reproductive age women. It occurs less frequently than cervical adenocarcinoma, and its prognosis is also better. This case study focuses on the conventional cytology sample of a 48-year-old woman, performed in the context of a screening programme at a health center of the Local Health Unit of Matosinhos.

The objective of this study is to verify the importance of the collection method used for cytological samples for a better observation and interpretation of the cytological findings related to rare neoplasias, as well as to reinforce the importance of performing complementary exams to reach a conclusive diagnosis.

In this case, the cytological result was atypical glandular cells (AGC) of endocervical type. Subsequently, the patient underwent a cervical biopsy, a conization of the cervix and an endocervical curettage, which resulted in a histological diagnosis of well differentiated villoglandular adenocarcinoma of the endocervix.

Key-words: well-differentiated villoglandular adenocarcinoma, endocervix, conventional cytology, screening

INTRODUCTION

The relative frequency of adenocarcinoma has been increasing, mainly because of the decreased frequency of invasive squamous cell carcinomas, contrarily to the past, where nearly 95% of the invasive cervical carcinomas were squamous cell carcinomas and only 5% were adenocarcinomas[1].

Patients with adenocarcinoma and squamous cell carcinoma have similar symptoms, with nearly 75% suffering from vaginal discharge and vaginal bleeding. Epidemiologically, the risk factors for both are also identical: more than 5 years after the last Pap smear test, multiple sexual partners, early sexual initiation, history of genital infections, obesity and smoking habits. Besides, the literature points that nearly 60% of adenocarcinomas are associated with low grade intraepithelial lesions or invasive squamous cell carcinomas[2].

Around 90% of all adenocarcinomas are associated with the human papillomavirus (HPV), with type 18 being the most frequent[1].

Endocervical villoglandular adenocarcinoma is a rare subtype of cervical adenocarcinoma, representing only 9% of its histological subtypes[2]. In opposition to the classic endocervical adenocarcinoma, this subtype affects mainly women in reproductive age; besides, it is less frequent and it has a better prognosis[3].

The villoglandular adenocarcinoma of the endocervix is a well-differentiated carcinoma with papillary architecture, resembling the villoglandular adenocarcinoma of the colon and the primary endometrial adenocarcinoma[1]. It is characterized by an exophytic proliferation with extensive and narrow papillary structures and mild to moderate cellular atypia. Because it is a well-differentiated tumor, cellular atypia might not be too obvious in the cytological analysis, which might lead to the result of a benign lesion[4].

A final diagnosis of endocervical villoglandular adenocarcinoma requires previous confirmation through histology[3]; however, it is important to understand if the cytology is sufficient to identify this rare type of glandular lesion.

CLINICAL HISTORY

This case is about a conventional cervicovaginal cytology from a 48-year-old woman, performed in the context of a screening programme carried out at a health center of the Local Health Unit of Matosinhos. Being a conventional cytology, it was not possible to detect an HPV infection in the sample.

After the attribution of a cytological result, the patient underwent a cervical biopsy, followed by a conization and a uterine curettage. The histological diagnosis required the patient to be submitted to a hysterectomy with right unilateral adnexectomy.

CYTOLOGICAL FINDINGS

The conventional cervicovaginal cytology sample was obscured by blood; however, it was possible to identify the presence of a mature squamous epithelium and abundant polymorphonuclear neutrophils (**Fig. 1A**). There were also some noticeable three-dimensional groups of glandular-like cells which were cytomorphologically compatible with endocervical cells (**Fig. 1B**). These cell groups were cohesive and had a papillary conformation, with visible and mostly regular borders; nuclear overlapping, pseudo-stratified epithelium and feathering were also observed, as well as tumor diathesis in the background (**Fig. 1** and **Fig. 2**).

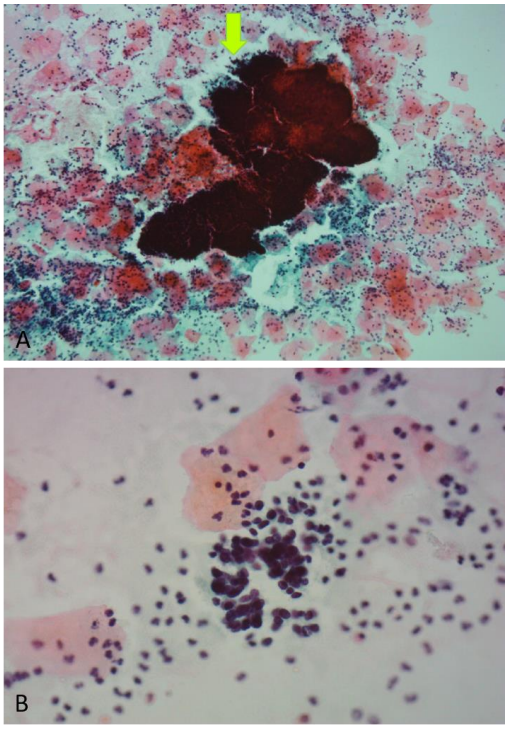

Fig. 1 – Cervicovaginal cytology with atypical glandular cells of endocervical type (AGC): **A –** Papillary-like group of endocervical cells obscured by blood. Increased nuclear-cytoplasmic ratio, hyperchromatic nuclei and feathering (arrow). Polymorphonuclear cells in the background (10x); **B**- Group of endocervical cells with scarce cytoplasm, hyperchromatic nuclei, pseudo-glandular arrangement (100x). Conventional smear, Papanicolaou stain.

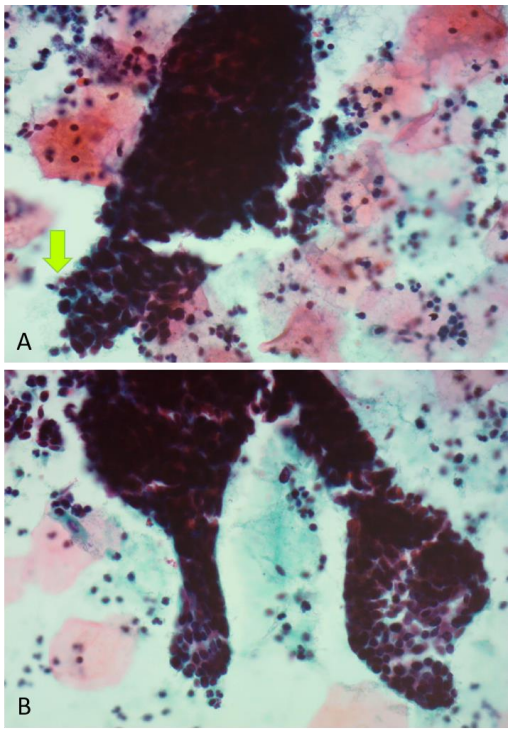

Fig. 2 – Atypical glandular cells (AGC) of endocervical type: **A**- Group of endocervical cells with high nuclear-cytoplasmic ratio, nuclear hyperchromasia and irregular nuclear membrane. Feathering (arrow); **B**- Papillary-like group of endocervical cells with hyperchromatic nuclei and high nuclear-cytoplasmic ratio. Tumor diathesis. Conventional smear, *Papanicolaou* stain, 40x.

The papillary-like cell groups were particularly striking, due to the intense hyperchromasia of their nuclei (**Fig. 2**).

Also regarding the nuclei characteristics, and besides the small increase of their size, one could also observe some irregularity in the nuclear membrane and evident nucleoli in some cells. The cytoplasm was generally scarce, and the nuclear-cytoplasmic ratio was high (**Fig. 3**).

INITIAL DIAGNOSIS

The cytological characteristics described above led to a result of atypical glandular cells (AGC) of endocervical type. Besides the nuclear atypia, the inflammatory background with some diathesis and the presence of typical papillary formations that exceed a normal pattern of reactive and reparative changes, not every criterion for a cytological diagnosis of endocervical adenocarcinoma in situ or invasive adenocarcinoma was met. These neoplasias have, among other features, increased nuclear size, hyperchromasia, irregular chromatin, pseudo-stratification, feathering and mitotic activity (in the case of the endocervical adenocarcinoma *in situ*) and increased pleomorphic nuclei, irregular chromatin, presence of macronucleoli and evident tumor diathesis (in the case of the invasive endocervical adenocarcinoma).

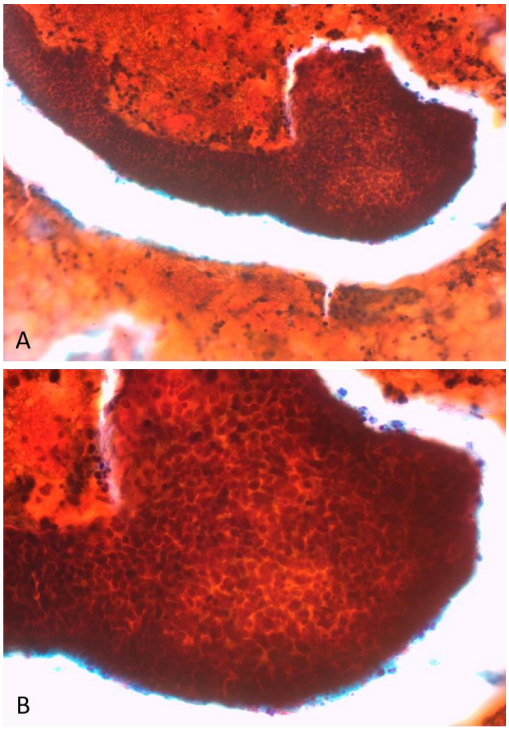

Fig. 3 – Atypical glandular cells (AGC) of endocervical type; **A-** Cohesive papillary formation, increased nuclear-cytoplasmic ratio, hyperchromatic nuclei, hematic background (20x); **B**- Cohesive papillary formation, increased nuclear-cytoplasmic ratio, hyperchromatic nuclei, hematic background. Highest magnification (100x). Conventional smear. *Papanicolaou* stain.

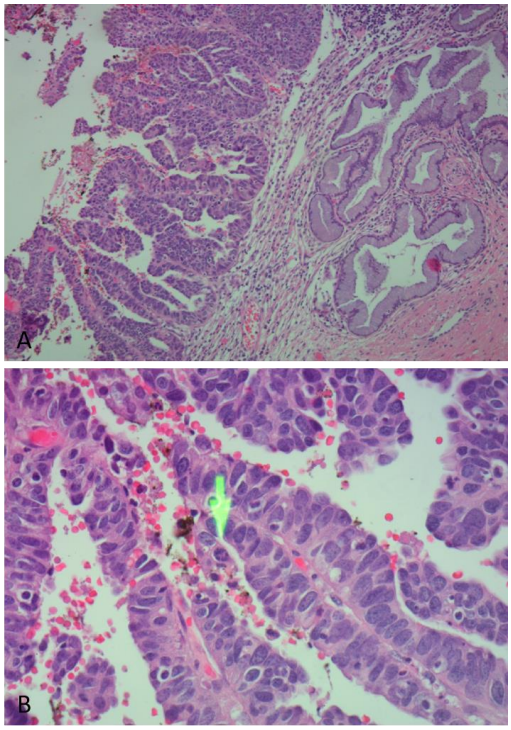

Fig. 4 – Histological features of the villoglandular adenocarcinoma: **A**- Villoglandular growth, coexisting with normal endocervical glands (10x); **B**- A higher magnification reveals a differentiation typical of a villoglandular adenocarcinoma, with mitotic figures and apoptotic bodies linked to the cytopathic effect of the HPV infection (40x). Cone biopsy specimen. Haematoxylin-eosin stain.

HISTOLOGICAL FINDINGS

The histological analysis to the cone biopsy specimen allowed to observe a portion of the cervix that encompassed the transition zone, with lesions characteristic of a microinvasive villoglandular adenocarcinoma of endocervical type (with less than 3 mm of depth and no more than 7 mm of size) coexisting with normal endocervical glands (**Fig. 4A).** Besides the evident mitotic figures, we also observed the presence of apoptotic bodies that appeared in association with the cytopathic effect of the HPV infection[1] (**Fig. 4B**). No images of vascular permeability were found.

In addition, there were segments of tissue with high grade intraepithelial lesion (CIN3) extensive to the glands, as well as cytopathic changes associated with the HPV infection.

DISCUSSION AND CONCLUSION

The villoglandular adenocarcinoma is a well-differentiated type of cervical adenocarcinoma. It is very rare, and its prognosis is usually more favorable than that of some traditional adenocarcinomas, due to its low progression and rare lymphovascular invasion[6]. Only a few studies show relapses of this subtype of cervical cancer after a long-term follow-up[4]. Despite affecting women of different ages, it appears mostly in younger women and women in reproductive age when compared to other subtypes of cervical adenocarcinoma. There are, however, studies showing cases in

women aged between 40 and 70 years[3], as it happened in this case which refers to a 48 year-old woman.

A screening through cytology is not, by itself, sufficient to diagnose a villoglandular adenocarcinoma, since the histological diagnosis is needed. However, despite the indistinct cytological features and the apparently mild cellular atypia[4], the cytological analysis raised enough information for a diagnosis of suspicion of malignancy and, consequently, it suggests that more comprehensive exams should be performed.

Cervicovaginal cytology is still the most effective method to prevent cervical cancer[7]. However, conventional smears present some limitations, namely in regards to the utility of the collected material and the overlapping of cell components[8]. Besides, the presence of some elements like blood and mucus makes it more difficult to observe the smear through microscope and might compromise the cytological result, thus adding to the number of limitations of the conventional cytology for the diagnosis of cervical lesions[9,10].

In this case, the excessive amount of blood resulted in an obscuring of most of the sample; the fact that the cytological sample was prepared through a conventional smear also made it more difficult to reach a conclusive diagnosis. The choice for a liquid-based cytology can be an advantage in these cases, as it is more sensitive and specific when identifying endocervical glandular lesions when compared to the conventional cytology[11].

In previous studies, the liquid-based cytology allowed to make a diagnosis of villoglandular adenocarcinoma, enabling the observation of the specific cytomorphological features of this entity, such as three-dimensional papillary clusters with well-defined contours, nuclear overlapping, pseudo-stratification and also some isolated cells with an increased nuclear-cytoplasmic ratio, nuclear hyperchromasia, prominent nucleoli and rare mitotic figures[4,12].

The conventional smear cytology result was AGC of endocervical type, with nuclear atypia that exceeded the cytological pattern of reactive and reparative changes, but proved insufficient to make a diagnosis of endocervical adenocarcinoma in situ or invasive adenocarcinoma. However, the sample also exhibited three-dimensional groups of cells with considerable pseudo-stratification, slightly hyperchromatic nuclei and indistinct nucleolus; these features are compatible with a diagnosis of endocervical AGC[5].

The cervicovaginal cytology is, in general, an important and relatively effective method for the prevention and early detection of squamous carcinomas. However, there is no consensus regarding its effectiveness in detecting cervical adenocarcinomas, with several factors hindering a precise detection of glandular lesions. One of those main factors lies in the collection procedure, which depends on the location of the glandular epithelium. Thus, if the lesion is inside the cervical glands or on the endocervical canal, its identification through a cytological sample is more difficult. Such difficulties often lead to the attribution of differential diagnosis that include AGC, high-grade squamous intraepithelial lesion (HSIL), presence of endometrial cells, follicular cervicitis and tubal metaplasia[4,13]. Given the low sensitivity of the cytology for the detection of glandular lesions, other complementary examinations become necessary, namely histological analyses and HPV detection tests. The well-differentiated pattern of the villoglandular adenocarcinoma subtype makes its recognition in cytology more difficult, due to the less obvious atypia of its cells[4,13]. Despite the frequent association between HPV and this subtype of adenocarcinoma, in this case the HPV detection test was not possible to performed.

In view of the foregoing, this case study is aimed at alerting cytotechnicians and pathologists for the need to increase experience, diagnostic skills and more sensitivity for the identification of the cytological characteristics related to this type of glandular lesions.

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