Vaginal cytology with suspicion of squamous intraepithelial lesion of undetermined grade: a case report

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ABSTRACT

This article reports a case of a 42 year-old female patient diagnosed in 2011 with adenocarcinoma *in situ* and severe cervical intraepithelial neoplasia that was treated with trachelectomy.

In November 2013 a vaginal vault cytology was performed, with cytological findings consistent with low-grade squamous intraepithelial lesion but also with the presence of cells that favour the diagnosis of high-grade intraepithelial lesion. Since it was not possible to grade the lesion as clearly low or high, it was attributed the result of squamous intraepithelial lesion of undetermined grade.

In order to confirm and clarify the diagnosis, a biopsy was performed which showed results of severe squamous intraepithelial neoplasia without evidence of stromal invasion. Finally, the specimen was tested for human papillomavirus genotype, with a positive result for type 16.

Cytologic diagnosis of intraepithelial lesions of undetermined grade present histologic outcomes that are statistically different from intraepithelial lesions of high and low grade, and are mostly associated with infection by high-risk human papillomavirus. This findings support retaining intraepithelial lesions of undetermined grade as a unique category in the *Bethesda* System, and define the management guidelines for this patients.

Key-words: Undetermined-grade Squamous Intraepithelial Lesion; Severe Dysplasia; Human Papillomavirus type 16

BACKGROUND

A 42 year old woman assisted on November 2011, with a history of adenocarcinoma *in situ* (AIS) and severe dysplasia in the squamous epithelium of the cervix (CIN III), was treated surgically with a trachelectomy in a different hospital on April 2012. On November 2013, the same patient was submitted to a cytology of the vaginal apex - a liquid-based cytology (*ThinPrep*), stained with *Papanicolaou* staining. In the obtained preparation was possible to observe scarce material, cytolysis and a large amount of *Döderlein* bacilli, containing some cellular groups and individual cells suggesting a Squamous Intraepithelial Lesion (SIL) (**Fig.1 A-C**). Some mature cells were also observed, with abundant cytoplasm of polygonal shape, slightly enlarged nuclei (until three times the actual size of an intermediary cell), binucleations (**Fig. 1A** and **1B**), and nuclear hyperchromasia with typical cavitation of cytopathic effects caused by infection with human papillomavirus (HPV) (**Fig. 1C**).

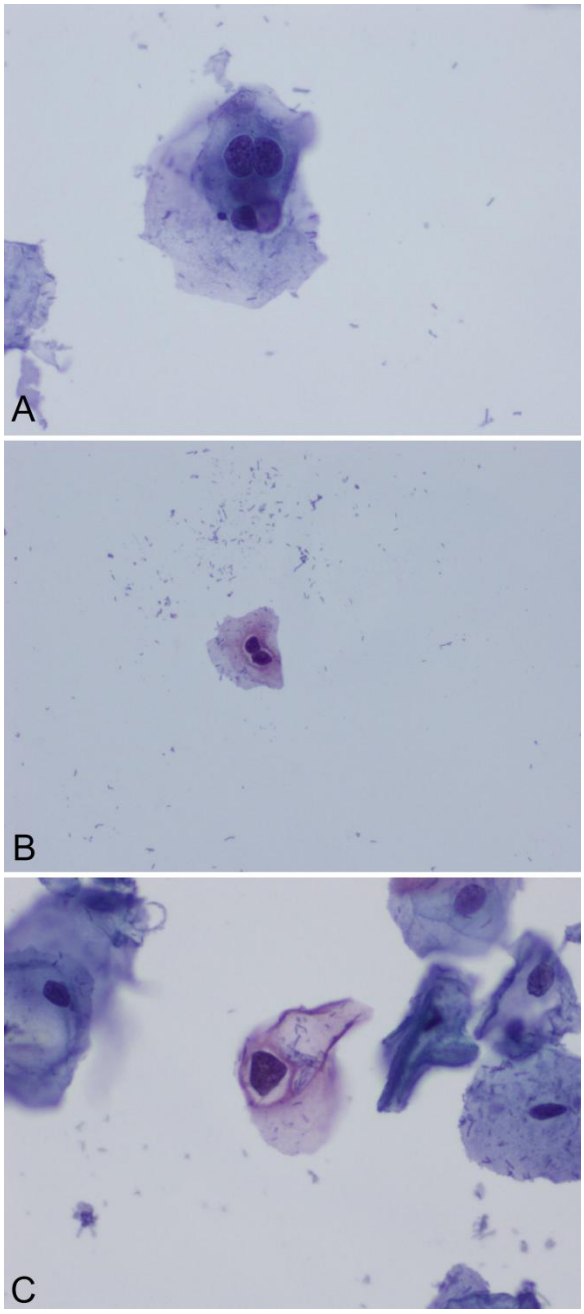

Fig.1 - Liquid-based cytology (*ThinPrep*). *Papanicolaou* stain (880x, **A** and **C**; 440x, **B**)

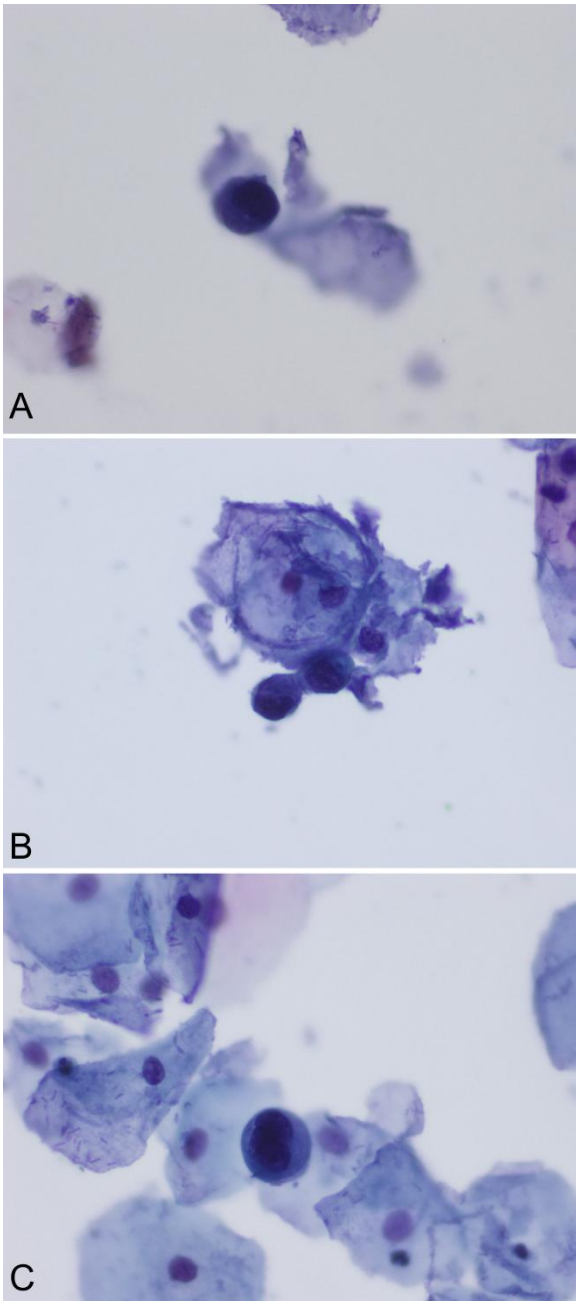

Fig.2 - Liquid-based cytology (*ThinPrep*). *Papanicolaou* stain (880x, **A**, **B** and **C**)

These findings lead to the diagnosis of Low-grade Squamous Intraepithelial Lesion (LSIL)[1]. On the other hand, the cytologists also found immature individual cells, smaller and with rounded edges, dense and metaplastic cytoplasm, significant increase in the nucleus/cytoplasm ratio, irregular nuclear membrane, hyperchromatic nuclei, as well as vastly granular and unequally distributed chromatin (**Fig. 2A** and **C**), leading to the diagnosis of High-grade Squamous Intraepithelial Lesion (HSIL)[1].

Groups of immature cells were also identified, which might have conducted to the diagnosis of HSIL, with an increase in the nucleus/cytoplasm ratio and slight nuclear changes, specifically hyperchromasia, irregularities on the membrane and nucleus enlargement (**Fig. 3A** and **3B**).

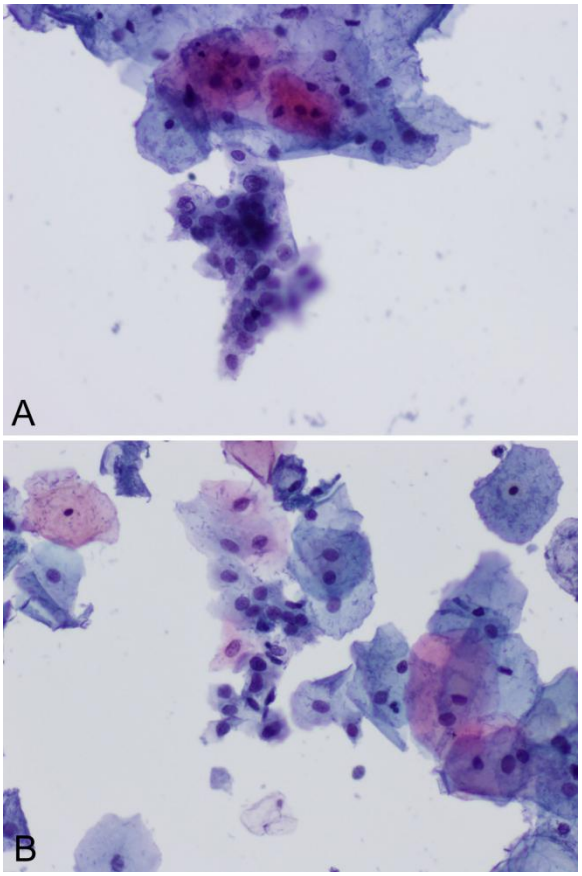

Fig.3 - Liquid-based Cytology (*ThinPrep*). *Papanicolaou* stain (440x, **A** and **B**)

INITIAL DIAGNOSIS

According to the aforementioned cytological findings, the initial diagnosis was supposed to be LSIL or HSIL. However, the morphologic characteristics observed in this case lead to and support a SIL of undetermined grade result.

ANALYSIS AND DISCUSSION

The lesions on the squamous epithelium of the cervix are classified in two categories, according to the *Bethesda System,* reviewed in 2001: LSIL and HSIL[1]. Nevertheless, it is known the existence of some cases in which the intraepithelial lesion is not possible to categorize as being of low or high grade. In such cases, the designation of Undetermined Grade SIL is appropriate, despite not being acknowledged by the *Bethesda System*[1].

Undetermined Grade SIL is equivalent to the 'LSIL cannot exclude HISL' (LSIL-H) and the 'LSIL with atypical squamous cells cannot exclude HSIL' (LSIL+ASC-H) categories[2,3], leading, therefore, to either LSIL or HSIL classifications[1]. This type of lesion is characterized by the presence of mature cells with abundant cytoplasm of polygonal shape, nucleus enlargement until three times the nuclear size of a common intermediary cell, and nuclear hyperchromasia with possible cavitation typical of cytopathic effect caused by HPV infection[1]. The characteristics that support the diagnosis of HSIL include immature cells, with cytoplasm varying from delicate to dense/metaplastic, increase in the nucleus/cytoplasm ratio, irregular nuclear membrane, rough and unequally distributed chromatine[1].

While evaluating this case, the hypothesis of Atypical Squamous Cells cannot exclude HSIL (ASC-H) was abandoned, since this category demands the absence of cells with LSIL characteristics. The main difficulty concerning the attribution of a final diagnosis was to understand if the cytological findings were sufficient to diagnose HSIL, or if the real condition was LSIL. The scarcity of the material, associated with the presence of few cells with HSIL-characteristics, prevented the attribution of this result. At the same time, the existence of such cells made impossible a diagnosis of only LSIL.

In order to confirm and clarify the diagnosis, the patient was submitted to a biopsy of the vaginal apex, which result was a serious Vaginal Intraepithelial Neoplasia (VAIN II/III), without evidence of stromal invasion. In addition to this, a slide reviewing was solicited to the institution where the patient was previously monitored, which allowed to witness that the histological findings were similar to the ones previously obtained. As a consequence of the matching of the two diagnoses, the result of VAIN III with no evidence of stromal invasion was attributed. On account of this, the analysis and HPV genotyping was suggested, which result was positive for the type 16.

While evaluating the histological follow-up of SIL of Undetermined Grade, several studies demonstrated that this type of lesion has an associated risk of including CIN II or CIN III between the cytological diagnosis of LSIL and HSIL[3-8]. A recent study showed that 22,8% of the cytological diagnosis of Undetermined Grade SIL are linked to a histological *follow-up* of CIN (Grade II or higher), which is 2,6 times superior to the one obtained among patients with cytological diagnosis of LSIL (8,3%), but also three times smaller than the one obtained among patients with cytological diagnosis of HSIL (69,3%). In this extent, Undetermined Grade SIL emerges as being statistically different, situated in an intermediary level between the two main categories of intraepithelial lesion[3].

Besides this, a pattern has been noticed concerning the distribution of infection by HPV, revealing a great risk associated with Undetermined Grade SIL[9]. The ratio of high-risk infection by HPV among patients with this type of lesion (92%) is superior to the one obtained among patients with LSIL (74%), and very similar to the one obtained among HSIL cases (91%). However, the most common carcinogenic genotype, HPV 16, was present in 36% of the patients suffering from Undetermined Grade SIL, which is inferior to the ratio obtained among patients with HSIL (44,6 %)[9].

Another pertinent aspect to be considered concerning this type of lesion is that, despite being briefly described in the *Bethesda System* of 2001, there are no guidelines on the 2006 consensus and neither on the update made by the *American Society for Colposcopy and Cervical Pathology* in what concerns to the *follow-up* applicable to these situations[10,11]. The absence of guidelines might cause uncertainty among practitioners, concerning the guidance that they should provide to their patients.

Since the cytological results of Undetermined Grade SIL represent a risk of including CIN II or CIN III, it is advisable to take on a follow-up similar to the one applied in LSIL cases. The approach should comprise more aggressive methods, namely a colposcopy with biopsy[3].

Considering all the details previously exposed, specifically the distinct histological follow-up in-between the two lesion categories defined as diagnosis, a pattern of high risk infection by HPV and absence of guidelines on the guidance provided to patients, several authors consider that Undetermined Grade SIL should be acknowledged as a new diagnostic category by the *Bethesda System*[3-5,8,9,12].

CONCLUSION

In the current case, the final cytological result was reported as: Undetermined Grade SIL, later confirmed by a biopsy with a VAIN II/III result, with no evidence of stromal invasion. This category should be attributed only in the presence of cells with morphological changes linked to LSIL simultaneously with cells suspicious for HSIL, never upon the existence of unequivocal findings of HSIL.

Even though Undetermined Grade SIL is not regarded as a valid diagnosis by the *Bethesda System*, numerous pathologists attribute this category to cases where the degree of the epithelial lesion is not clearly defined. Although uncommon, such cases may lead to the establishment of a new diagnostic category, as it has proved to be clinically different from the ones already defined.

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