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Minimal Deviation Adenocarcinoma Associated with High-Grade Squamous Cervical Intraepithelial Neoplasia

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Abstract

Background: Minimal deviation adenocarcinoma of the cervix is a rare neoplasm of difficult diagnosis due to its histological features, which are suggestive of being benign and seldom associated to Human Papilloma Virus (HPV).

Clinical case: We present the case of a 46 year old Mexican patient referred to our institution for the presence of abnormal cervical cytology, confirmed by biopsy of cervical squamous cell carcinoma *in situ*, who underwent cervical cone biopsy, which reported a minimal deviation adenocarcinoma 13mm in length and 7mm in depth with adenocarcinoma ans squeamous cell carcinoma *in situ* in the endocervical margins. The patient was undertaken to a Type C2 radical hysterectomy and a Level 2 bilateral lymphadenectomy plus bilateral salpingoophorectomy.

In the final pathology report no residual lesion was identified. The patient remains disease-free at follow-up.

Conclusions: The association of minimal deviation adenocarcinoma with a high-grade cervical intraepithelial neoplasm and high-risk papillomavirus is a rare event.

Keywords

Cancer of the uterine cervix, Adenoma malignum, Cervical intraepithelial neoplasm

Introduction

Cancer of the uterine cervix is the second cause of cancer at the worldwide level in women, with an incidence of 529,409 new cases annually and is the third place in mortality with 274,883 deaths; in Mexico it represents the second cause of cancer in women with 10,186 new cases each year and the second cause of cancer-related mortality with 5,061 cases, second only to breast cancer [1].

Most cervical epithelial cancers are squamous cell, adenocarcinoma of the cervix represents from 20-25% of all cervical carcinomas; within this subgroup is found minimal deviation adenocarcinoma, which represents 1-3% of all adenocarcinomas of the uterine cervix [2,3].

Squamous and glandular lesions are a frequent association; the proportion of adenocarcinomas *in situ* associated with intraepithelial neoplasms with high-grade squamous cervical intraepithelial neoplasms ranges from 24-75%, because both are found to be associated to Human papillomavirus (HPV) infection and are thought to be originated from the same reserve-cell type. However, minimal deviation adenocarcinoma is a neoplasm that is not associated with HPV infection, suggesting that may be originated from endocervical glandular hyperplasia, thus the rarity of its association with Cervical Intraepithelial Neoplasia (CIN) [4].

The objective of this case is to show the diagnostic difficulty that

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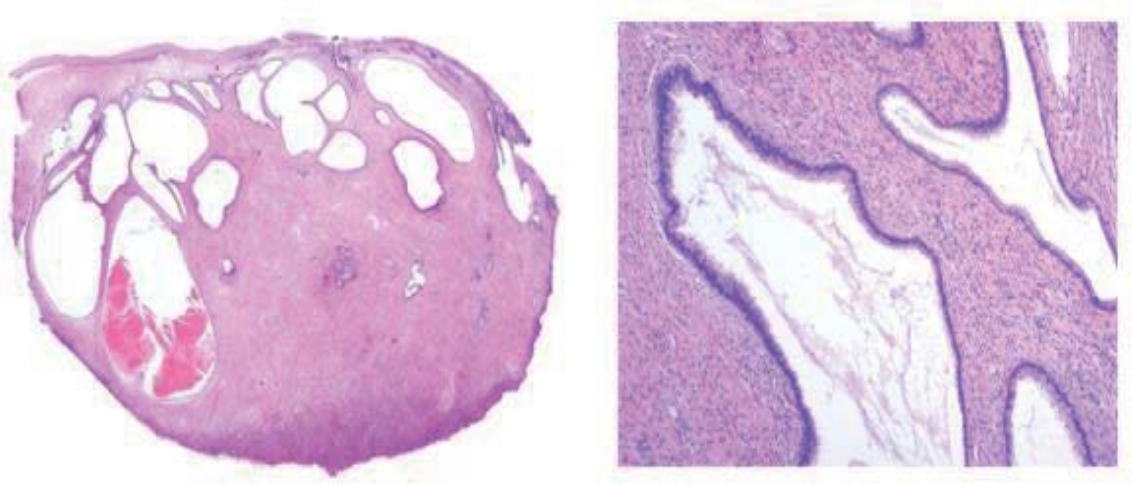

Figure 1: Deep gland extension to stroma in cone specimen.

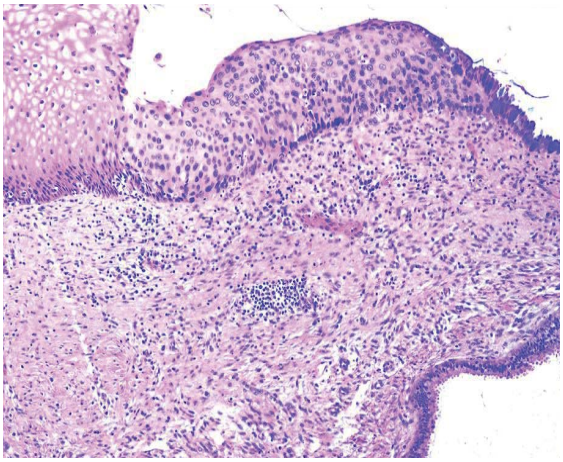

Figure 2: HE 20X component of *in situ* squamous cell carcinoma.

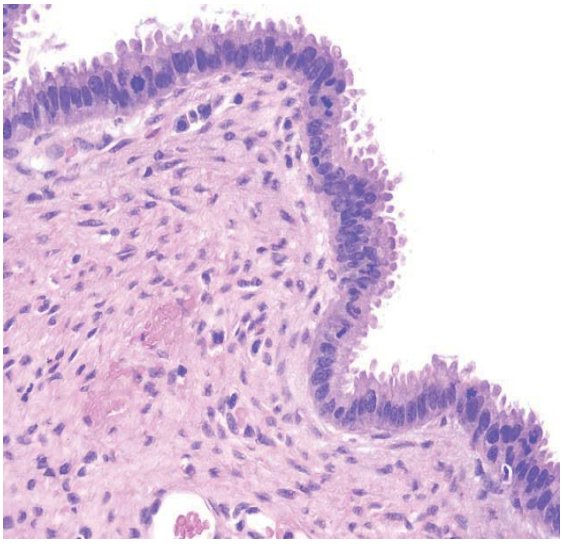

Figure 3 : HE 40X minimal deviation adenocarcinoma, notice endocervical epithelium with mild atypia and frequent mitosis.

this combination of neoplasms may represent to the surgeons as well as for the pathologists.

Clinical Case

This case concerns a Mexican female patient aged 46 years, without

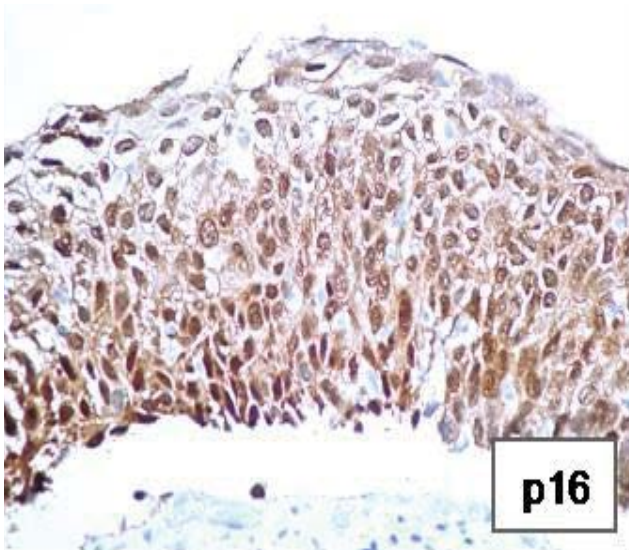

Figure 4: P16 stain. Positive in abnormal squamous epithelium and negative in minimal deviation adenocarcinoma.

relevant medical or familial history, she was referred to the National Institute of Cancerology of Mexico (INCan) in January 2009 due to uterine cervix cytological screening test with the report of High-grade Squamous Intraepithelial lesion (HSIL). The colposcopic examination was considered abnormal due to the presence of an acetowhite lesion in the transformation zone that included the endocervical canal. The remainder of the colposcopic and pelvic examination was considered within normal limits. Cervical cytology reported an HSIL and the biopsy of squamous cell carcinoma *in situ* of the uterine cervix. A cone biopsy was performed and considered as therapeutic in March 2009. The final histopathological report of the cone was minimal deviation-type endocervical adenocarcinoma, tumor size was 13mm of horizontal extension and 7mm of depth of invasion, with neoplasm on the endocervical border and deep stromal border associated with squamous cell carcinoma *in situ*; the exocervical border was reported as neoplasm-free. (Figure 1-3).

Immunohistochemistry was positive for P16, in HSIL and negative in endocervical adenocarcinoma. Ki67 was high in endocervical adenocarcinoma and HSIL components (Figure 4).

With the previous report, the patient was staged as having an adenocarcinoma of the uterine cervix clinical stage Ib1. Extension studies were negative for metastasis and a decision was made to carry out a Type C2 radical hysterectomy and a Level 2 bilateral lymphadenectomy [5] plus bilateral salpingoophorectomy in April

2009, without complications, with the patient discharged from the hospital on postoperative day 3.

The final Pathology report revealed inflammation and cervical metaplasia without evidence of residual disease, 18 pelvic lymph nodes with hyperplasia without evidence of neoplastic cells, with the surgical-resection borders reported as negative for intraepithelial lesion.

During follow-up, HPV infection was documented in the vaginal cytology; hybrid capture was positive for high-risk HPV. Conservative treatment just with close follow-up was decided upon and at the patient's last visit in January 2012, colposcopy and vaginal cytology was found without lesions, solely reporting unspecific inflammatory changes.

Discussion

Minimal deviation adenocarcinoma (MDA) of the uterine cervix is a rare neoplasia that is difficult to diagnose, was described for the first time in 1870; the term minimal deviation was coined in 1975 by Hurt and Silverberg [2,3].

The risk factors for this neoplasm are scarcely clear; despite the important relationship of HPV, mainly VPH 16 and -18, with carcinogenesis of the uterine cervix, in reports on MDA a relationship with the virus has not been identified [6-8]. What has been found is a relationship with the Peutz-Jeghers syndrome; in one series, 4 of 27 women with the latter syndrome developed MDA [9] and with lobular endocervical hyperplasia.

Average age at diagnosis is 45 years (range, 20–78 years); the clinical manifestations presented by the patients are the following: in 69.4% of cases, there is the presence of an aqueous or mucoid vaginal secretion; 50% of patients present irregular or abnormal vaginal bleeding, and in 24.5% of cases there is pelvic pain or urinary obstruction. In the majority of patients, the cervix tends to be thickened or with hypertrophy on macroscopic examination [8,10].

Cervical cytology as a diagnostic method for MDA has a detection rate of only 32.7% (10), with infrequent diagnosis by this method due to the well differentiated characteristics of the tumor cells in which there is scarce observation of atypias and the absence of a marker that could be used for differentiating tumor cells from the normal ones, as well as the scarce frequency of the neoplasm, which makes it not to be suspected [11]. Due to that these lesions tend to be found in deep cervical layers, it is necessary to perform large biopsies with at least 7mm depth or greater, or to perform cervical cone biopsy to confirm the diagnosis [12].

In the report of Li et al. [10], 50.7% detection was documented with the performance of cervical biopsies in 185 patients and 100% detection in the 14 patients on whom cervical cone was carried out, therefore it seems that a cervical cone is the most reliable method to perform an accurate diagnosis.

The definitive diagnosis is based on the histopathological characteristics with the presence of glands varying in size and shape covered with a columnar epithelium with mucoproducer cytoplasm, predominately baseline nucleus or slight atypia, and the presence of stromal invasion. Most important for suspicion of the diagnosis is the localization of the glands below the level where these are normally found, that is, at a depth of >7mm; thus, it is important to take deep biopsies or even to perform a cervical cone in order to obtain a good sample of the lesion. Another histological datum that is of aid in diagnosis is the presence of mitosis in the apical part of the glands, because mitoses are very infrequent in normal endocervical epithelium.

The tumor-suppressor gene *STK11* has been identified as responsible for the Peutz-Jeghers syndrome, an autosomal dominant disorder characterized by gastrointestinal hamartomatous polyps and mucocutaneous pigmentation, as a possible triggering effect in the development of MDA due to *STK11* gene mutation and/or the loss of heterozygosity at the 19p13.3 locus of the gene [13,14].

Imaging studies such as transvaginal Ultrasound (US) as well as Computed Tomography (CT) tend to present multicystic cervical lesions, while by Magnetic Resonance Imaging (MRI) T2 sequence it is observed that in the majority of cases the presence of fine, non-cystic villi or hyperintense, multicystic lesions that extend from the endocervical glands to the deep stoma of the cervix [15]. In the report of Itoh et al., on comparing the three techniques, the authors showed that MRI revealed the most detailed characteristics and best correlation with the histology [16]; however, differentiation or identification by lesion type is highly complicated, above all because multicystic lesions are easily confused with benign changes in the uterine cervix, such as Naboth´s cysts.

The co-existing presentation of an HSIL together with this adenocarcinoma variant is very rare, as previously mentioned [17], and due to the different carcinogenesis pathways, we infer that these are coincidental rather than related neoplasms.

Treatment for MDA is similar to that for any other adenocarcinoma of the cervix, limiting it to surgical treatment based on a Type C2 radical hysterectomy and a Level 2 bilateral lymphadenectomy (5) plus bilateral salpingoophorectomy at early clinical disease stages, as was performed in our patient, and similarly, it can be observed that the disease recurrence rate is influenced by the clinical stage. Chemotherapy plus radiotherapy is reserved for treatment at locally advanced clinical stages.

Conclusions

Minimal deviation adenocarcinoma of the uterine cervix is an entity that represents a challenge in terms of diagnosis, due to the low frequency of the neoplasm as well as to the histological complexity, it has been suggested by Gong et al that this tumor is a real neoplasm because of its clonal origin as well as it has not been related to HPV infection [18].

The combination of a HSIL associated with MDA is a much less frequent combination, which will render the clinician's initial treatment of the patient as if it were an adenocarcinoma *in situ*, which in the final analysis will not make the proposed treatment the adequate one.

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