SYMPOSIUM CANCER OF THE CERVIX UTERI

1. Oncological Pathologist, Research Professor, Universidad San Martín de Porres, Lima, Perú. Director Pathology Department Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru. ORCID 0000-0002-0914-9149. Scopus Author ID 6504431054. Web of Science IWD-7494-2023

Conflicts of interest: The author declares no conflict of interest.

Funding: Self-funded.

Declaration of use of artificial intelligence: No artificial intelligence-related technology was used in the research and/or in the preparation of this article.

Received: 8 October 2024

Accepted: 11 October 2024

Online publication: 14 December 2024

Corresponding author:
Luis Taxa
labtaxa@gmail.com

Cite as: Taxa L. Premalignant lesions and cervical cancer unrelated to human papillomavirus. Rev peru ginecol obstet. 2024;70(4). DOI: https://doi.org/10.31403/rpgo.v70i2694

Premalignant lesions and cervical cancer unrelated to human papillomavirus

Lesiones premalignas y cáncer de cuello uterino no relacionados al virus del papiloma humano

Luis Taxa[1]

DOI: https://doi.org/10.31403/rpgo.v70i2694

ABSTRACT

Cervical cancer is the second most common malignancy in Peruvian women. The new WHO classification divides cervical epithelial neoplasms according to the presence or absence of human papillomavirus (HPV) for both squamous and glandular types. Much has been studied on HPV-related cervical cancer and little in HPV-negative cervical cancer, which, although representing a minority group, is of different behavior and worse prognosis. This review represents an overview of this pathological with emphasis on molecular aspects. Undoubtedly, with the research of this pathology group and mainly molecular development, more specific treatments are expected.

Key words: Cervical cancer, Human papillomavirus, Histology, Pathology, Prognosis

RESUMEN

El cáncer de cuello uterino es la segunda neoplasia maligna más frecuente en la mujer peruana. La nueva clasificación de la OMS divide a las neoplasias epiteliales de cuello uterino en función de la presencia o no del virus del papiloma humano (VPH), tanto para la forma escamosa como glandular. Se ha estudiado mucho el cáncer de cuello uterino relacionado al VPH y poco el que es negativo para VPH que, aunque representa un grupo minoritario, es de diferente comportamiento y peor pronóstico. La presente revisión representa una visión general de esta patología haciendo hincapié sobre los aspectos moleculares. Indudablemente, con la investigación de este grupo patológico y principalmente el desarrollo molecular se esperan tratamientos más específicos.

Palabras clave. Cáncer del cuello uterino, Papillomavirus humano, Histología, Patología, Pronóstico

Introducción

Cervical cancer is the second most frequent malignant neoplasm in Peruvian women[1,2], a very unfortunate fact because unlike other neoplasms it can be prevented. Since the 1950s, there has been a simple method such as the Pap smear which, within a structured program and with good quality control standards, has allowed developed countries to control this disease. In developing countries such as ours it has not been possible to prevent it, and we still have a high percentage of advanced cervical cancer[2].

According to the new WHO classification, cervical epithelial neoplasms are classified according to the presence or absence of the oncogenic virus responsible for the development of the carcinoma, whether epidermoid or adenocarcinoma, depending on whether the exocervical or endocervical component is the origin of the neoplasm[3].

Epithelial neoplasms generally develop from precursor lesions, known as squamous intraepithelial lesions (SIL), from which neoplasms progressively emerge. It is at this stage that we must target resources in their detection in order to cut off the natural progression of the disease. Regarding the pathogenic mechanisms of these precursor lesions, it was known that they originate from infection by the human papillomavirus, which is divided into low-risk and high-risk groups[4]. High-risk papillo-

mas are mainly those which, through persistent infection, manage to incorporate and control the genes responsible for the cell cycle[5]. Thus, they manage to progress not only at the molecular level, but also alter the histological structure from low-grade to high-grade squamous intraepithelial lesions. If left undetected at this stage, it will inexorably progress to an invasive stage.

Ming Zhao et al[6] conducted a meta-analysis of persistent HPV infection in women worldwide. From a total of 28 studies with 27,335 participants they found that persistent infection constituted 29.37% and the genotypes with prevalence of persistent infection were HPV16 (35.01%), HPV52 (28.19%), HPV58 (27.06%), HPV18 (25.99%), HPV33 (24.37%), HPV31 (23.35%), HPV59 (21.87%), HPV39 (19.54%), HPV68 (16.61%) and HPV45 (15.05%). The prevalence of multiple and single persistent HPV infection was 48.66% and 36.71%, respectively. It was concluded that multiple infections were more likely to result in persistent HPV infection than single infection.

This is true for most squamous lesions (98%) and a large percentage of glandular lesions (around 80%). However, little is known about non-HPV-related lesions. Among them, non-HPV-related adenocarcinomas have been the most studied, the precursor lesion being adenocarcinoma *in situ*[7], and among invasive non-HPV-related adenocarcinomas the most representative type is gastric adenocarcinoma[8,9]. Little is known about non-HPV-related squamous lesions.

Clinico-molecular features of non-HPV squamous cell carcinomas

They are rare neoplasms and account for around 2%. Their incidence increases with age, from 65 years onwards. They are aggressive neoplasms, are detected in advanced stages and are often resistant to conventional management[10,11]. Furthermore, the presence of HPV is not detected in these neoplasms, and they are negative by indirect immunohistochemical methods - for example, the study of p16 - as well as by molecular studies. It has been observed that these squamous neoplasms often have p53 mutations. A smaller number of cases are HPV(-)/p53(Wild Type). Thus, there are researchers who propose two subtypes of non-HPV related squamous carcinomas: p53 mutated type and p53 WT[12].

Riou et al, in 1990, were the first to describe in a series of 106 cases and by molecular methods the presence of high-risk HPV in 86% of them. But they also reported that, when compared with HPV-negative cases, these were at higher risk of relapse and distant metastasis, with statistical significance. Based on this experience, they argue that HPV-negative invasive carcinomas represent a biologically distinct group of tumours with a worse prognosis[13].

Danqing Li et al, in 2022, in a cohort of 729 patients previously screened with molecular methods detected 40 HPV-negative patients. They performed a new molecular study including PCR and continuous hybridization for 37 HPV types, of which the absence of HPV was confirmed in 13 patients, concluding in this group a higher stage of disease, lymph node metastasis, larger size and a higher proportion of adenocarcinomas; in short, with a worse prognosis[14].

Clinico-molecular characteristics of non-HPV adenocarcinomas

Non-HPV-related adenocarcinomas of the uterine cervix represent a heterogeneous group of neoplasms that, unlike squamous carcinomas, account for 15-20% of cervical carcinomas. Although the main criterion for diagnosis is a negative molecular test for HPV, it could be a case of false-negative HPV due to a failure in the pre-analytical management, an insensitive molecular method with a low viral load for detection, or even that the cause of the lesion is a low-risk HPV, as has been described[15].

They are subdivided into gastric, clear cell, mesonephric and endometrioid types.

Gastric adenocarcinoma is the most common type, accounting for approximately 10% of all adenocarcinomas of the uterine cervix. To this type belongs the previously known as minimal deviation adenocarcinoma, which is the well-differentiated form of the gastric type, which is difficult to diagnose on superficial biopsy and even more difficult on cytology. A precursor lesion is now recognized as lobular endocervical glandular hyperplasia (LEGH), sometimes associated with Peutz-Jeghers syndrome, which progresses to dysplastic change, subsequently giving rise to adenocarcinoma[16,17]. These lesions are macros-

copically characterized by being tumors that can have a polypoid appearance (Figure 1) or ulcerated. Microscopically, they are characterized by a glandular pattern, with deep distribution in a "claw" shape (Figure 2), with little desmoplastic reaction. The cells are columnar, mucinous, with pale to pink cytoplasm, few apical mitoses, generally well-differentiated.

Genetic mutations have been described, such as alterations in P53, STK11, KRAS, among others, even linked to precursor lesions. By using immunohistochemistry, these tumors commonly express HIK1083, MUC6, PAX8, CAIX, CEA, and CK7. The prognosis shows that they are aggressive lesions, being in most cases diagnosed in advanced stages (II-IV) and with distant metastasis, especially to the lung, ovary, liver, colon and bone[18].

Clear cell carcinomas account for 2%-7% of adenocarcinomas. Although their etiology is unknown, they have been reported in women whose mothers have consumed DES (diethylstilbestrol). The peak incidence is reached in the second decade of life and remains high for life[19]. Cases not associated with DES are frequently associated with endometriosis, and 25%-30% are associated with HPV[20]. These tumors present as exophytic or endophytic masses without a characteristic appearance. Microscopically they

Figure 1. Tumor with a polypoid appearance protruding from the uterine cervix into the vagina, with abundant mucoid secretion (LOT case photo).

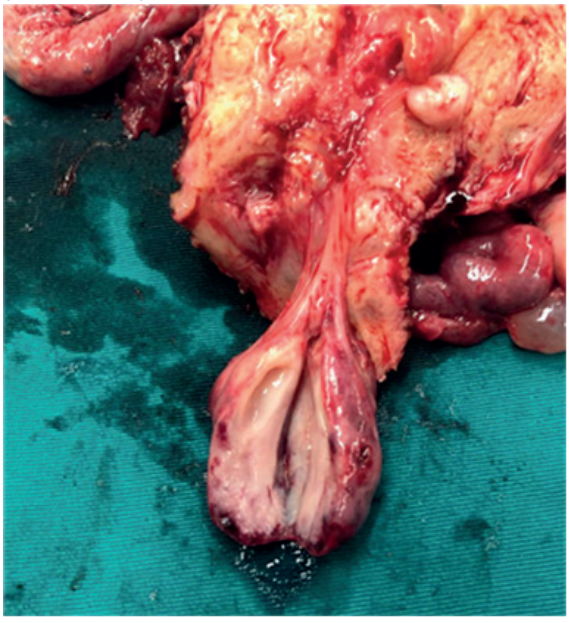
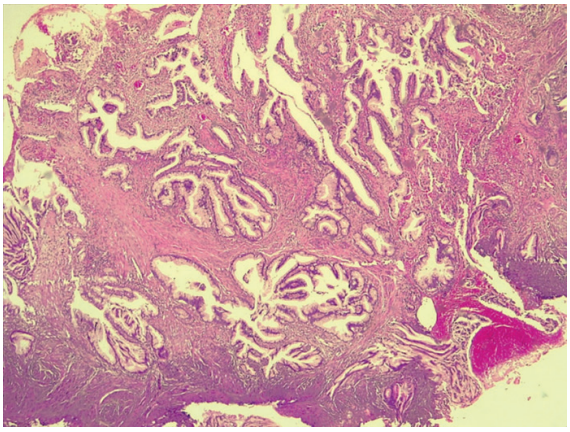


Figure 2. Histological findings correspond to a well-differentiated gastric adenocarcinoma (ex-malignant adenoma). This case even metastasized to the ovary, indicating its aggressive behavior, despite being a well-differentiated lesion (LOT case photo).



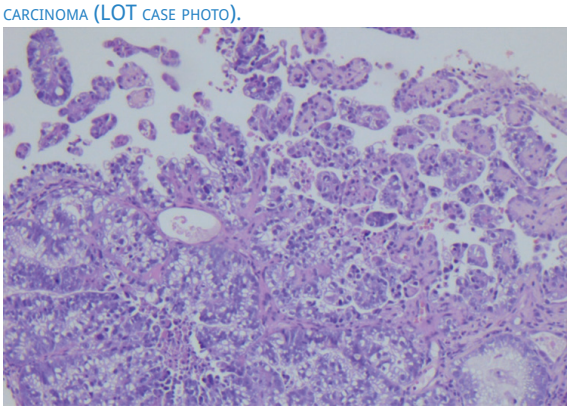
are characterized by a tubulocystic, papillary, and/or solid pattern, lined by cells with generally clear to eosinophilic cytoplasm, with the nuclei arranged towards the lumen of the gland like 'tacks' (Figure 3). They express HNF1β, Napsyn A and AMACR by immunohistochemistry. The prognosis is usually aggressive[21].

Mesonephric adenocarcinomas are non-HPV-related neoplasms that develop between the ages of 35 and 72. They are located in the lateral area of the uterine cervix, as they would originate from mesonephric remnants that suffer KRAS mutations and gain in chromosome 1q. They are neoplasms that express immunohistochemical markers such as GATA 3 and CD 10[22], are aggressive and have a poor prognosis.

Endometrioid adenocarcinomas of the uterine cervix are the least frequent, accounting for less than 1%. These neoplasms are thought to originate from cervical endometriosis. Macroscopically, they are tumor masses, and microscopically, they have an appearance similar to endometrium, with glands lined by tall cells with stratified nuclei, with or without squamous differentiation. The differential diagnosis is with endometrioid adenocarcinomas of the endometrium, so immunohistochemistry is used to a limited extent in the intended differential diagnosis (P16, ER and GATA3), since there is no specific marker that allows for that difference[23].

In sum, non-HPV-related epithelial neoplasms of the uterine cervix constitute a group of neoplasms that must be confirmed by immunohistochemical and molecular methods. They are

Figure 3. 46-year-old female patient presenting with abnormal uterine hemorrhage. On examination, the cervix was tumorous with parametrial involvement. Histology corresponds to a clear cell carcinoma (LOT case photo).



less frequent, more aggressive and are detected in more advanced stages, so they have a worse prognosis, which should be considered for more aggressive management.

Conclusions

Non-HPV cervical cancer has a more aggressive behavior compared to HPV-positive types, both in the squamous and glandular forms, and the molecular characteristics are different. New treatment modalities are expected to be developed based on these differences.

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