Immunohistochemical investigation of p-53, C-NEU and EGFR expression in HPV-related epidermoid endometrial carcinoma

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Summary

Epidermoid carcinoma (PSCC) of the endometrium is a rare form of endometrial cancer that constitutes about 0.1% of all malignant epithelial tumors of the uterus. The diagnosis of PSCC is based on strict criteria and is made in the absence of a glandular component of the tumor.

Squamous cell carcinoma of the endometrium should enter the differential diagnosis in postmenopausal patients in the presence of atypical squamous cells in the uterine curettage, while the cervical biopsies are negative for malignancy. The presence of HPV should be investigated as well, so that its pathogenetic relation is clarified. While no significant relation was found to p-53, C-NEU and EGFR expression this investigation must be continued because. HPV may interact with tumor suppressor genes.

Key words: Epidermoidal endometrial carcinoma; Squamous cell carcinoma; HPV; p-53; C-NEU; EGFR.

Introduction

Epidermoid carcinoma of the endometrium is a rare form of endometrial cancer that constitutes about 0.1% of all malignant epithelial tumors of the uterus [1]. The diagnosis of epidermoid carcinoma is based on strict criteria and is made in the absence of a glandular component of the tumor, of continuity with cervical squamous epithelium or of any connection with a cervical primary neoplasm [2, 3]. About 30 cases of epidermoid carcinoma are reported and its prognosis is poor, with 40% of the patients in pathological stage I, dying of the tumor within three years after diagnosis [3].

Some cases are associated with cervical stenosis, pyometra, endometrial squamous metaplasia or with squamous cells arising on mullerian remnants in the endometrium [4]. Its pathogenesis remains obscure and its relationship with HPV infection is under investigation as well as the interaction between the HPV sequences and certain cellular oncogenes such as tumor suppressor genes (p-53) or growth factors (EGFR, C-NEU) [5, 6].

In this case report we investigated the presence of certain HPV types as well as the expression of p-53, C-NEU and EGFR.

Case Report

A 72-year-old woman was admitted to the 2nd Obstetrical and Gynecological Unit of Areteion University Hospital for metrorrhagias and uterine prolapse.

The Pap test was negative for malignancy while diagnostic curettage showed abundant keratin masses with parakeratosis as well as cervical fragments showing inflammation. No endometrial tissue was found in the curretings.

A total hysterectomy with both adnexa was performed and the histological study showed an atrophic uterus measuring 8x6.5x5 cm. The cervix was normal while the endometrial cavity and the uterine wall were infiltrated extensively by a well-differentiated squamous cell carcinoma that infiltrated focally the whole thickness of the uterus (Figure 1). Some atrophic endometrial glands

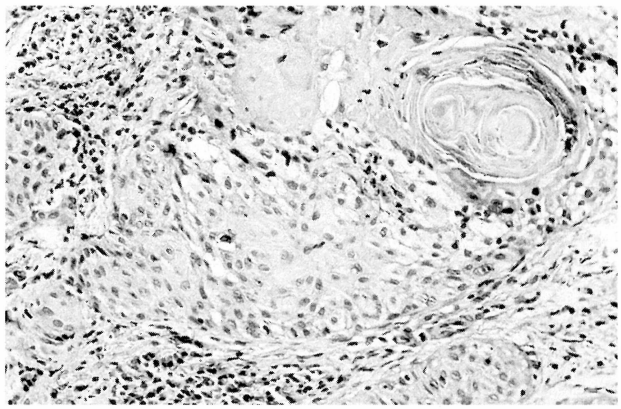

Figure 1. — Histological section of uterine tumor with morphology of epidermoid carcinoma (H-E x 25).

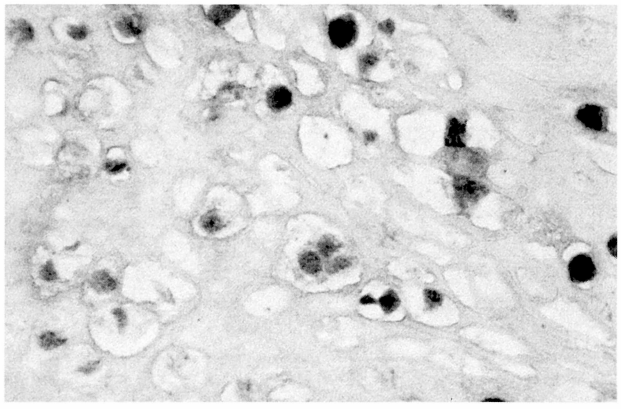

Figure 2. — Histological section of uterine epidermoid carcinoma showing positive reaction for HPV 31-33 (H-E x 250).

Revised manuscript accepted for publication June 22, 2001

remained covered by metaplastic squamous cell epithelium. The cervical transformation zone presented mature squamous cell metaplasia that in no place reached the endometrial cavity. The right ovary presented a fibroma. No secondary neoplastic deposits were observed at the time of surgery. The patient underwent adjuvant chemotherapy. She died a year later from causes unrelated to her neoplastic disease.

Immunohistochemical study by in situ hybridization showed positivity for HPV types 31-33 (Figure 2). The expression of p-53 protein (SKYTEK D07, SKYTEK, USA), C-NEU (CB11, NOVOCASTRA) and EGFR ($EGFR_1$, NOVOCASTRA) was investigated by a streptavidin-alkaline phosphatase-immunohistochemical method and revealed no expression of p-53 suppressor gene, C-NEU oncogene or EGFR.

Discussion

Primary epidermoid carcinoma of the endometrium is a rare neoplasm that arises in metaplastic changes of the endometrial mucosa. This metaplasia may be the result of a chronic inflammation, hormonic disturbance or uterine proptosis [1, 2, 7, 8].

All reported cases refer to postmenopausal women with painless metrorrhagia. Pyometra is a common symptom and is probably the result of cervical canal obstruction by the neoplasm.

The disease is usually diagnosed in advanced stage with extensive infiltration of the myometrium and peritoneal cavity.

In our case the existence of HPV DNA and especially of the 31-33 types (which are observed in high-grade cervical SIL and infiltrating squamous cell carcinoma) suggests that there may be a pathogenetic role of the virus, analogous to that in the pathogenesis of cervical or vulvar neoplasias [9, 10].

Variants of this virus may interact in different ways with host genetic factors, and this may alter the course of the disease. Thus, HPV 31/33 variants may differ in their ability to degrade p-53 and on the other hand polymorphic p-53 alleles may provide a less susceptible substrate for these viral oncogene products.

p-53 protein is a product of a suppressor gene located on the short arm of chromosome 17. Mutation of this gene will result in mutant p-53 protein which has no suppressor action. Wild type p-53 may accumulate by complexing with other proteins such as the oncoprotein of certain HPV types. The exact mechanism of this relationship is under investigation but there are reports that in high-risk HPV infected cells a genomic instability is promoted, leading to the acquisition of additional genetic changes leading to carcinogenesis [5, 11].

Recent experiments provide evidence for direct inter-action between specific HPV variants and p-53. Specifically the E6-gene oncoprotein of HPV types 16-18 has been shown to bind the tumor suppressor protein p-53 and this binding appears to promote the degradation of p-53 [5, 11, 12].

Human C-NEU oncogene sharing a tyrosine kinase activity and structural similarities to the epidermal growth factor receptor may be important in the initiation and/or progression of several human malignancies such as breast and ovarian cancer. EGFR is a potent mitogen for normal or malignant epithelia and there is a significant correlation between its increased expression and tumor progression [6, 12].

In invasive squamous cell cárcinomas of the cervix there is a loss of C-NEU expression while EGFR expression is common and was observed in most of the cancers studied. The biological or clinical importance of these findings is still unclear and our results may be added to the data concerning the etiology and progression of this rare form of endometrial cancer. An initial sequence analysis of HPV may be useful in monitoring variants that may play a role in the transformation of the host cell and subsequent carcinogenesis.

Therapy of epidermoid endometrial carcinoma consists of surgical hysterectomy with the adnexa and radiotherapy.

In conclusion, squamous cell carcinoma of the endometrium should enter the differential diagnosis of postmenopausal patients in the presence of atypical squamous cells in the uterine curettage, while the cervical biopsies are negative for malignancy. The presence of HPV should be investigated as well, so that its pathogenetic relation is clarified. While no significant relation was found to p-53, C-NEU and EGFR expression this investigation must be continued in view of the fact that HPV may interact with tumor suppressor genes.

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