Case report

Sarcomatoid squamous cell carcinoma of the uterine cervix: immunohistochemistry demonstrates an HPV-related tumor with epithelial origin

Carcinomul cervical infiltrativ scuamos de tip sarcomatoid: profilul imunohistochimic demonstrează originea epitelială și asocierea cu infecția cu HPV

Gavrilas Muresan¹, Kinga E Szabo², Laura Bejan², Cristina Marian², Monica Boros³, Nicolae Costin⁴, Simona Stolnicu²*

¹. Sanovil Clinic, Bistrița Romania
². Department of Pathology, University of Medicine, Tîrgu Mureș, Romania
³. Department of Pathology, Emergency County Hospital, Oradea, Romania
⁴. Department of Gynecology and Obstetrics Dominic Stanca, University of Medicine, Cluj-Napoca, Romania

Abstract

Sarcomatoid squamous cell carcinoma (SSCS) is a well-documented entity but occurs rarely in the female genital tract, with only 20 reported cases in the uterine cervix. A 72 years old patient was diagnosed with a polypoid 4 cm diameter cervical tumor. Microscopically, the tumor was composed of a poorly differentiated classic keratinizing squamous carcinoma, which was associated with a well-delineated, secondary, extensive and heterogeneous sarcomatoid component. An abrupt transition between the two components was observed, with no zones of gradual transition. The positivity of the sarcoma-like component for epithelial markers (CAM5.2, AE1/AE3, CK5/6) and p16 favors a common epithelial squamous origin of both components of the lesion and an association with HPV- infection. This diagnostic immunophenotype excluded other malignant cervical tumors with a true mesenchymal component that may have different treatment and prognosis.

Keywords: sarcomatoid squamous cell carcinoma, cervix

Rezumat

Carcinomul scuamos de tip sarcomatoid (CSS) reprezintă o leziune distinctă ce se dezvoltă mai frecvent în alte organe, mai rar în tractul genital feminin, până în prezent fiind publicate doar 20 de astfel de cazuri cu localizare cervicală. Prezentăm cazul unei paciențe de 72 de ani diagnosticată cu o formăție tumorală polipoidă cervicală cu diametru de 4 cm. Microscopic, tumora a fost constituită dintr-un carcinom scuamos infiltrativ clasic keratinizat slab diferențiat asociat cu o a doua componentă de tip sarcomatoid, cu caracter extensiv, heterogen, între cele două componente fi-

*Corresponding author address: Prof. Univ. Dr. Simona Stolnicu, Department of Pathology, University of Medicine Targu Mures, Str. Gh. Marinescu nr. 38, E-mail: stolnicu@gmx.net
Introduction

Sarcomatoid squamous cell carcinoma (SSCS) is a well-documented entity in the oral cavity, pharynx, esophagus and larynx but rarely occurs in the female genital tract, with only 20 reported cases in the uterine cervix (1-8, 11, 12). Usually, a recognizable squamous cell carcinoma merges with a spindle cell component. We present a SSCS in a 72 years old patient with an abrupt transition between two distinct components on microscopic examination and in whom a diagnostic immunophenotype excluded other malignant tumors that may have different treatment and prognosis and confirmed both epithelial origin of the tumor and the association with HPV infection.

Case report

A 72-year-old woman had massive abnormal vaginal bleeding due to a cervical mass. Due to the lack of a national screening programme in Romania and the age of the patient, no previous Pap smear was examined in the last 10 years in this patient and no history of a previous cervical lesion was known. A biopsy was performed and a diagnosis of a high grade sarcoma of the cervix was initially established. She was referred to the Gynecologic Oncology Clinic and was treated with total hysterectomy with bilateral salpingo-oophorectomy and pelvic and paraaortic lymphadenectomy. Macroscopically, the cervical examination revealed a 4 cm soft, irregular, polypoid tumor that was infiltrating the full thickness of the cervical wall. The uterine corpus and adnexa were unremarkable and three of the 20 regional lymph nodes that were surgically removed were enlarged. Microscopically, approximately 50% of the tumor was composed of a poorly differentiated classic keratinizing squamous carcinoma, which was associated with a well-delineated, secondary extensive and heterogeneous sarcomatoid component. An abrupt transition between the two components was observed, with no zones of gradual transition. The sarcomatoid tumor cells had either a spindle shape and were arranged in fascicles being reminiscent of sarcomas such as fibrosarcoma, leiomyosarcoma or a round/polygonal shape with abundant eosinophilic cytoplasm, marked atypical nuclei, frequent mitotic figures, arranged in a loose fashion, suggesting a rhabdomyosarcoma (Figure 1). No osteoclast-like cells or other malignant heterologous elements such as chondrosarcoma or osteosarcoma were seen within the tumor. Immunohistochemically, both components had a similar phenotype, as they were positive for cytokeratins as CAM5.2, AE1/AE3, CK5/6, but also for p63, suggesting an epithelial and squamous identity (Figure 2). Actin, H-Caldesmon, Desmin and Myogenin were negative in both components and Vimentin was only positive in the sarcomatoid component.

P 16 was positive in both components and PCR demonstrated the presence of HPV16 suggesting that this type of tumor develops in association with HPV infection (Figure 3). The ki-67 index was very high with more than 90% of the tumor cells positive for both components (all markers for immunohistochemical studies were provided by DAKO, Glostrup Denmark, and were prediluted). The cervical squamous epithelium overlying the tumor or lining the entrapped endocervical glands within the tumor...
Figure 1. The tumor is composed by a squamous component (A, HE, x4) with an abrupt transition to a second sarcomatoid component (B, HE, x4) which is composed by either spindle tumor cells (C, HE, x10) or large polygonal cells (D, HE, x20); large cell nonkeratinizing squamous carcinoma component along with spindle cell or large polygonal cell morphology (E, HE, x10); the polygonal shape cells with abundant eosinophilic cytoplasm, marked atypical nuclei, frequent mitotic figures, arranged in a loose fashion with stromal edema (F, HE, x20).
disclosed the presence of extensive cervical intraepithelial neoplasia (CIN) grade III (Figure 4). Several tumor emboli were observed adjacent to the tumor but also involving the blood vessels of the isthmus. Extensive areas of necrosis were observed within the tumor. The final diagnosis was sarcomatoid squamous cell carcinoma (SSCC) of the cervix. The tumor was associated with lymph node metastases in 3 out of 20 regional lymph nodes. The patient was planned for concurrent chemoradiation therapy but only received 2 cycles of chemotherapy and died 4 weeks postoperatively due to renal failure.

Discussion

80% of the infiltrating carcinomas of the cervix are of squamous type and usually associated with HPV infection, while 10-20% of them are of glandular type and among these, 10% are not associated with an HPV infection similarly to other rare types of sarcoma, lymphoma, melanoma or metastatic tumors (4, 9). SSCC is a rare and aggressive variant of the infiltrating squamous carcinoma that is not recognized by the WHO classification in 2003 (10). Few cases have been described so far in the female genital tract (11, 12) with only 20 cases that have been reported in the cervix, most of them being diagnosed in an advanced stage at presentation and characterized by early recurrence following treatment and short disease-free survival (1- 8). The tumor is also called spindle cell squamous carcinoma, and it consists in a classic infiltrative squamous carcinoma admixed with a second spindle cell compon-
ent, that is typically of high grade. The tumor contains both components, which usually blend subtly. In our case, two completely separate components were seen, each representing 50% of the tumor, one of classic keratinizing squamous type and a second one composed of either spindle or large polygonal type cells, marked nuclear atypicality and stromal edema suggesting a carcinosarcoma (malignant mullerian mixed tumor – MMMT). Carcinosarcoma may have a prominent component of squamous cell carcinoma particularly in the cervix. However, the associations with a CIN III as well as the lack of other epithelial components (like adenocarcinoma) or other heterologous sarcomatous components favor a SSCC, although cervical carcinosarcoma may have an in situ squamous cell carcinoma component present within the tumor. Also, strong diffuse immunoreactivity of the sarcomatoid component for both epithelial markers (CAM 5.2, AE1/AE3) strongly suggests an SSCC (1). Interestingly, the sarcomatoid component can also co-express Vimentin, similarly to this case, and smooth muscle actin (1). The immunohistochemical stains must be interpreted with caution since the spindle cell component of the sarcomatoid carcinoma may be focally positive or negative for cytokeratins and the mesenchymal component of a carcinosarcoma can express cytokeratin occasionally.

The positivity of both epithelial and spindle cell component for p16 demonstrates an association with HPV infection, which in this case was also supported by the demonstration of HPV 16 on PCR. Similar findings were reported only once (6) in a 31 years old patient in which PCR and in situ hybridization studies revealed the presence of HPV type 16. This fact demonstrates that even rare and unusual subtypes of infiltrating squamous carcinoma are related with HPV infection and that these cases would benefit from the prophylactic HPV vaccination. In contrast, glandular lesions have rare and unusual subtypes, representing 10% of them, which are not associated with HPV infection (9).

Thus, despite the sarcomatoid appearance, SSCC is an entirely epithelial neoplasm, with no malignant mesenchymal component present within the tumor and which is also associated with HPV infection as the other squamous infiltrating carcinomas of the cervix, implying that the two diseases have the same etiology and are nothing but variants of the same entity.

Acknowledgement

The diagnostic contribution of Professor Francisco F. Nogales, University of Granada Spain is gratefully acknowledged in this case.
References