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Squamous cell carcinoma of the endometrium with contiguous superficial spreading to the vagina, uterine cervix, fallopian tube, and ovary

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Summary

The coexistence of cervical and endometrial surface squamous cell carcinoma (SCC) is extremely rare. A 63-year-old woman was referred to the present hospital because of an abnormal Pap smear indicating SCC. Biopsies from the vagina, ectocervix, and endocervix indicated SCC *in situ*, and endometrial curettage revealed SCC with stromal invasion. The patient underwent a radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. Microscopically, the SCC *in situ* exhibited extensive spread into the vagina, uterine cervix, endometrium, bilateral fallopian tubes, and left ovary. In addition, extensive stromal invasion into the uterine corpus was identified. Polymerase chain reaction revealed human papilloma virus (HPV) type 16 from biopsies from the uterine cervix, corpus, and vagina. SCC of the endometrium may arise secondarily to HPV infection and may spread, in some cases, superficially into the vagina, cervix, and adnexal organs. Additional studies are required to fully elucidate the precise mechanisms of carcinogenesis and tumor spreading in endometrial SCC.

Key words: Carcinogenesis; Endometrium; Human papilloma virus; Squamous cell carcinoma.

Introduction

Squamous cell carcinoma (SCC) of the uterine cervix is one of the most common gynecologic malignancies. It usually spreads by direct extension into the parametrium, and secondary endometrial involvement by cervical SCC occurs by a lymphatic route or by deep direct myometrial invasion [1, 2]. In addition, primary SCC of the endometrium (PSCCE) is extremely rare, with fewer than 100 cases reported in the literature [3]. The diagnostic criteria for PSCCE that has traditionally been used necessitated an absence of coexisting adenocarcinoma or adenosquamous carcinoma, a lack of connection between the tumor and squamous epithelium, an absence of concurrent or preexisting cervical SCC, and intercellular bridges, and/or keratinization as evidence of squamous differentiation [4, 5].

Endometrial surface SCC coexisting with cervical squamous neoplasia is extremely rare, and approximately 30 cases have been reported in the literature [2]. Interestingly, some cases were associated with microinvasive SCC or high-grade squamous intraepithelial lesions (HSIL) [1, 2, 6-9] that carry little or no risk of metastasis. Although a few of these cases exhibited invasion in upper genital lesions [1, 6, 8, 9], these invasions were interpreted as secondary to surface extensions from the uterine cervix because they failed to fulfill the diagnostic criteria for PSCCE. Herein, the authors report an unusual case of SCC that exhibited a contiguous superficial spread to the vagina, uterine cervix, uterine corpus, fallopian tubes, and ovary, with invasive foci in the uterine corpus.

Case Report

A 63-year-old, para 2, Japanese woman consulted a gynecologist due to vaginal bleeding over a year. She had been postmenopausal for five years. Her past medical history included an appendectomy and a cesarean section due to placenta previa at age 17 and 31, respectively. She was referred to this hospital because her Pap smear indicated an SCC. On admission, a speculum examination revealed a slightly ulcerated ectocervix with a white vaginal discharge. Colposcopy revealed acetowhite changes that extended to the vagina 1.5 cm from the vaginal fornices, suggesting vaginal invasion. Biopsies from the vagina, ectocervix, and endocervix indicated an SCC *in situ* (CIS), and a specimen from the endometrial curettage revealed an SCC with stromal invasion. Magnetic resonance imaging demonstrated endometrial thickening but failed to show any tumor in the uterine cervix (Figure 1). Her serum SCC antigen level was elevated to 6.8 ng/ml. These findings led us to presume that she had an endometrial and/or cervical SCC. She underwent a radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. Macroscopically, the uterus revealed a thickened and widened endometrial cavity with a gray white endometrium. A microscopic examination revealed a CIS with extensive spreading in the vagina, uterine cervix, endometrium, and bilateral fallopian tubes (Figure

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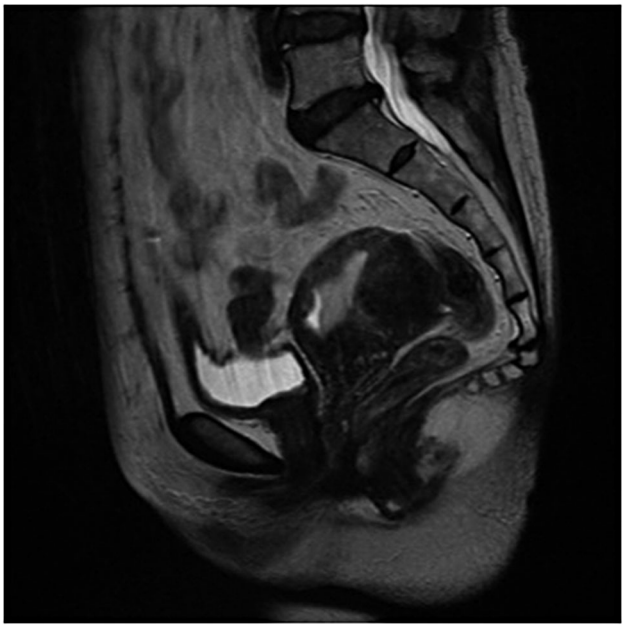

Figure 1. — Preoperative T2-weighted magnetic resonance imaging scan (sagittal section) demonstrating endometrial thickening that lacks a sharp endometrium-myometrium interface and posterior myometrial wall thickening suggesting adenomyosis.

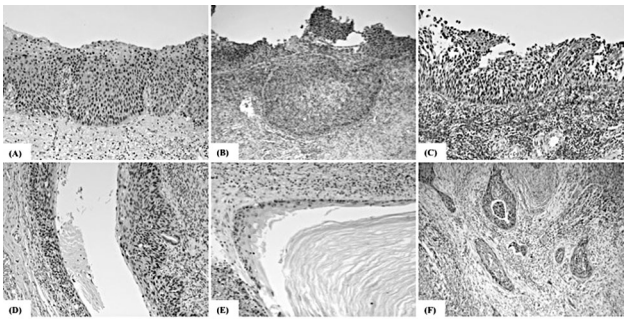

Figure 2. — Sections of the vagina (A), uterine cervix (B), endometrium (C), fallopian tube (D), and ovary (E) indicating contiguous superficial spread of squamous cell carcinoma (H&E staining, objective ×20). Cancer cells invade the myometrium (F) (H&E staining, objective ×10).

2A-D). In addition, the left ovary had small foci of SCC on its surface (Figure 2E). The endometrial glandular epithelium was almost completely replaced by superficial SCC, and cancer cells were found to be spreading in the myometrium, exhibiting a desmoplastic reaction (Figure 2F). The vaginal surgical resection margin was positive for CIS, and cytology of the ascites was positive for malignant cells. After surgery, she was given three cycles of adjuvant chemotherapy consisting of tegafur-uracil and cisplatin, along with intracavity brachytherapy. The patient has survived ten years postoperatively without evidence of disease.

Tissue samples were obtained from the uterine cervix, corpus, and vagina, and genomic DNA was extracted and examined for the presence of nine common anogenital human papilloma (HPV) viruses (types 6, 11, 16, 18, 31, 33, 42, 52, and 58). DNA analyses were performed to identify restriction fragment length polymorphisms, followed by polymerase chain reaction (PCR) amplification using the consensus primers for the L1 region as previously reported [10] by the SRL Laboratory. Tissue samples from the uterine cervix, corpus, and vagina were found to be positive for type 16 HPV.

Discussion

The coexistence of cervical squamous neoplasia and endometrial surface SCC is an extremely rare condition [2]. Although the mechanisms underlying the simultaneous development of SCC in different parts of the genital tract remain unknown, three possible histogenetic models have been proposed: 1) extension from the cervical cancer to upper genital tracts, 2) extension from the vagina, endometrium, fallopian tubes, or ovaries, and 3) multicentric occurrence in genital organs (a field effect) [8, 9]. Pins *et al.* [8] reported a case of cervical CIS with contiguous spread to the endometrium, fallopian tubes, and ovaries, with tubal and ovarian invasion. The investigators examined HPV DNA from cervical, endometrial, tubal, and ovarian tumors using PCR and detected HPV 16 in the samples from all sites, as observed in the present case. They hypothesized that an upward spread of the cervical tumor with subsequent upstream invasion was the most likely mechanism [8]. In addition, Kushima *et al.* [9] analyzed the allelic status of multiple tumor foci by loss of heterozygosity (LOH) analyses in five similar cases. These investigators demonstrated that homogeneous LOH throughout the micro-dissected lesions was most frequently detected on 6p and 6q, followed by 11p and 11q, loci that are commonly known to be lost in typical cervical SCC. They also found a genetic progression in terms of an additional LOH in the upper genital tract, but not in the cervix, in two of the five cases, and they concluded that these tumors originated from the cervix and extended superficially to the upper genital tract with genetic progression. However, these hypotheses pose a diagnostic dilemma to pathologists and gynecologists, because carcinogenesis generally occurs at the center of a tumor and stromal invasion is usually most pronounced at the center of a tumor.

The presence of squamous cells in the endometrial cavity is unusual and is considered to be the result of metaplasia of the endometrial glandular tissue. Chronic endometritis, hypovitaminosis A, estrogen deficiency and senile involution, previous radiation therapy, and presence of chemicals in the uterus are considered to be pathogenetic factors in squamous metaplasia of the endometrium [5]. A replacement of the entire surface of the endometrium by stratified squamous epithelium is an extremely rare condition and is referred to as “ichthyosis uteri”. Although ichthyosis is considered to be a benign condition, some investigators have speculated that PSCCE may arise from ichthyosis uteri [11-13]. Although the etiology of PSCCE remains unknown, some studies suggested that HPV may have played a role in the pathogenesis of PSCCE in some

cases [5,14]. In the present case, the endometrial glandular tissue was almost completely replaced by a superficially spreading SCC. Based on the literature and the present case, the present authors speculate that SCC may arise following HPV infection in the preexisting ichthyosis and extend into the vagina, cervix, fallopian tubes, and ovaries, although the present case failed to fulfill the diagnostic criteria for PSCCE. Recently, Yang *et al.* [15] reported an unusual case of multifocal micro-invasive SCC with extensive spreading of the CIS into the uterine corpus, cervix, salpinx, and vagina in a woman who had a history of cervical conization with a negative resection margin due to a CIS that occurred five years previously. They also assumed that the CIS in the endometrium may have spread back to the cervix and vagina. Additional studies are required to fully clarify the precise mechanisms of carcinogenesis and tumor spreading in endometrial SCC.

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