Papillary-serous Adenocarcinoma of the Uterine Cervix during Tamoxifen Therapy after Bilateral Breast Cancer

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Abstract. *Background: Papillary-serous adenocarcinoma (PSCC) is a very rare subtype of cervical cancer. To our knowledge, this is the first report on PSCC of the uterine cervix following bilateral breast cancer. Case Report: A 61-year-old Caucasian woman underwent conserving surgery of both breasts at the age of 57 years, because of bilateral invasive ductal carcinoma. Radiation and tamoxifen treatment followed. Routine surveillance examinations, including pelvic examination, Papanicolaou (Pap) smear, and transvaginal ultrasound, were uneventful. Recently, a small contact-bleeding mass of the cervix was found. The Pap smear was II (reactive); HPV-DNA test was negative. The biopsy of the mass revealed PSCC with a high expression of p53, carcinoembryonic antigen (CEA), and Ki67 (50%). Staining for estrogen receptor (ER), progesterone receptor (PR), and vimentin was negative. The serum carbohydrate antigen 125 (CA-125) reached 159 U/ml. The patient was treated with radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic and paraaortic lymphadenectomy. A poorly-differentiated papillary-serous, non-secretory adenocarcinoma, pT1b1, pN0 (0/44), pM0, G3, R0, V0, L0, was confirmed. According to the German recommendations for early-stage cervical cancer, the patient received no adjuvant treatment. Currently, the patient is free of relapse 38 months after the diagnosis of cervical cancer and 87 months after that of breast cancer. Conclusion: Immuno-histochemistry is helpful in diagnosing rare entities. This case adds further evidence that the prognosis for early-stage PSCC is probably not poorer than that for other cervical adenocarcinomas.*

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Papillary-serous adenocarcinoma (PSCC) is one of the rarest subtypes of cervical cancer. It is of Mullerian origin, with uncertain, very rare frequency (1, 2). Little is known about the clinical course of this type of cervical carcinoma because of its rarity. Based on about 60 reported cases, the prognosis for early-stage PSCC is probably similar to that for other cervical adenocarcinomas (3, 4). In contrast to cases of ovarian, tubal, and endometrial serous carcinoma, local (surgical) therapy for early PSCC does not seem to be inferior in terms of progression-free (PFS) or overall survival (OS) in comparison with surgery followed by adjuvant chemotherapy or radiation (3, 4). Although secondary cancer is generally common after breast cancer (an incidence of up to 14%), cervical cancer is very infrequent among them (5). Tamoxifen does not seem to promote the carcinogenesis of non-squamous cervical tumours. To the best of our knowledge, this is the first report on a serous adenocarcinoma of the uterine cervix following bilateral breast cancer.

Case Report

A 61-year-old Caucasian woman, primiparous, having reached menopause at 50 years, a non-smoker, and with no history of hormonal replacement therapy, was first diagnosed in 2005 with bilateral breast cancer at 57 years of age. The histology in both breasts showed an invasive ductal carcinoma: pT2, pN0 (0/1sn), G2, estrogen receptor (ER) 80%, progesterone receptor (PR) 60%, and human epidermal growth factor receptor 2 (c-ERBB2) score 0 for the right side; pT1a, pN0 (0/3sn), G1, and ER not determined for the left side. Treatment consisted of breast-conserving surgery for both sides, followed by radiation (60 Gy each side) and tamoxifen at 20 mg daily for 5 years. In the same year of diagnosis, a diagnostic dilatation and curettage was carried out because of a finding of Papanicolaou (Pap) III with endocervical cells (Munich nomenclature, *atypical glandular cells of undetermined significance* in the Bethesda classification), with no

indication for dysplasia or carcinoma in the final histology. The additional Hybrid-Capture-II-Test (Digene Corporation, MD, USA) was negative both for the presence of high-risk and low-risk HPV-DNA. Routine surveillance examinations, including pelvic examinations, Pap smears, and transvaginal scans, were uneventful in the subsequent four years. In 2009, a slightly contact-bleeding mass of the cervix with no other symptoms was found. The Pap smear was 'reactive' (class II in the Munich nomenclature), but the biopsy revealed a poorly- differentiated PSCC. The serum concentration of carbohydrate antigen 125 (CA-125) was elevated (159 U/ml), whereas the concentration of squamous cell carcinoma antigen (SCC) was within the normal range (0.80 ng/ml). Radical hysterectomy with bilateral salpingo-oophorectomy (Piver Class 2), and pelvic and para-aortic lymphadenectomy were performed. The gross examination revealed a tumour 25 mm in diameter, with an infiltration depth of 4 mm. The final examination confirmed the mass as being poorly- differentiated, non-secretory adenocarcinoma with papillary-serous growth patterns, along with portions of adenocarcinoma *in situ* (ACIS). The tumour exhibited a typical papillary architecture lined by cells with pleomorphic nuclei, numerous mitotic bodies, and psammoma bodies (Figure 1). The immunohistochemistry was negative for ER, PR, and vimentin, but highly positive for p53, carcinoembryonic antigen (CEA), and Ki67 (proliferative index of 50%). No further endometrial, myometrial, or ovarian pathology was seen. All removed lymph nodes (30 pelvic, 14 para-aortic) were negative for disease; the lymphovascular space was not invaded. The TNM classification was pT1b1, pN0 (0/44), pM0, G3, R0, V0, L0. According to the German recommendations for cervical cancer (6), adjuvant treatment is considered unnecessary for pT1b1/pN0. The CA-125 level fell to a normal value (<35 U/ml) after four months. The patient remains free of relapse 38 months after the first diagnosis of cervical cancer and 87 months after diagnosis of breast cancer.

Discussion

PSCC belongs to the rarest of cervical carcinomas. The histology is characterized by a complex pattern of papillae with cellular budding and the frequent presence of psammoma bodies. This makes it similar to its ovarian counterparts. Before a diagnosis of primary serous adenocarcinoma of the cervix is made, spreading from the endometrium, ovaries, or peritoneum should be excluded (7). PSCC should be distinguished from other papillary carcinomas with better-prognosis, such as low-grade papillary villoglandular adenocarcinoma (1). Immunohistochemistry plays a major role in the diagnosis of PSCC. Nofech-Mozes *et al*. stated that PSCC is a distinctive immunophenotypic subtype of endocervical adenocarcinoma with significantly higher p53 and lower CEA reactivity than other more common histological subtypes (1). In the presented case the tumour exhibited an abnormally high expression of p53. Strong and diffuse p53 positivity in PSCC may be useful in its differentiation from uterine endometrial adenocarcinoma (8). The lack of ER and vimentin expression further helped to disclose an endometrial origin. Bodner *et al*. found that in common-type cervical adenocarcinomas, neither the expression of ER nor the expression of PR had any influence on patient PFS or OS (9). The role of HPV infection in PSCC is unclear. HPV-DNA has been investigated in only 11 cases published so far, with the prevalence of HPV-DNA in PSCC being 55% (6/11). In the reported cases, HPV-DNA was detected in young women, but the causality seems to be speculative (high HPV prevalence *versus* rarity of PSCC) (10). In our case, the PSCC was associated with extensive ACIS. For the uterine corpus, an association of papillary serous carcinoma with serous endometrial intraepithelial carcinoma and glandular dysplasia was assumed. Remarkably, the pre-cancerous lesions had a high p53 staining and high Ki67 index scores (11). In the immunohistochemical study of Nofech-Mozes *et al*., only p53 and CEA immunostaining significantly correlated with the PSCC morphology (p=0.001 and p=0.016, respectively) (1). Similarly to our case, the leading symptoms in PSCC are abnormal genital bleeding or discharge in 76% to 92% of cases (3, 4). Abnormal cervical pathology occurred only in 8% to 24% of cases. Interestingly and similar to our case, most patients were diagnosed with disease at stage pT1b (3, 4), mostly at pT1b1. The 5-year OS seems to be determined by parametrial involvement and differs from 89% for stage pT1b (no parametrial involvement) to 0% for stage pT2b (spread to the parametria). Therefore, a radical hysterectomy should be obligatory for apparent early-stage PSCC. On the other hand, all patients with advanced-stage PSCC suffered recurrence, despite radical hysterectomy (4). Togami *et al*. concluded that patients with advanced-stage PSCC could have more aggressive tumour behaviour than those with common-type adenocarcinoma (4). Positive prognostic factors are age <45 years, stage I, tumour size <2 cm, depth of invasion <10 mm, and negative lymph nodes. Surprisingly, histological grade 2 *vs*. 3, pure *vs*. mixed-type, and positive p53 staining did not influence the prognosis (3). We used CA-125, the typical serum marker for serous cancer, for follow-up. The elevation of CA-125 (159 U/ml) indicates similarities with other serous carcinomas. Bender *et al*. found that a serum CA-125 level of ≥30 U/ml was an independent marker of poor prognosis for patients with cervical adenocarcinomas (12). The range of CA-125 in other cases was 90 to 2,480 U/ml (13, 14). In some case reports, PSCC was treated with carboplatin or carboplatin/paclitaxel combination, similar to therapy for other papillary-serous cancer (14). For ovarian cancer, the early normalisation of CA-

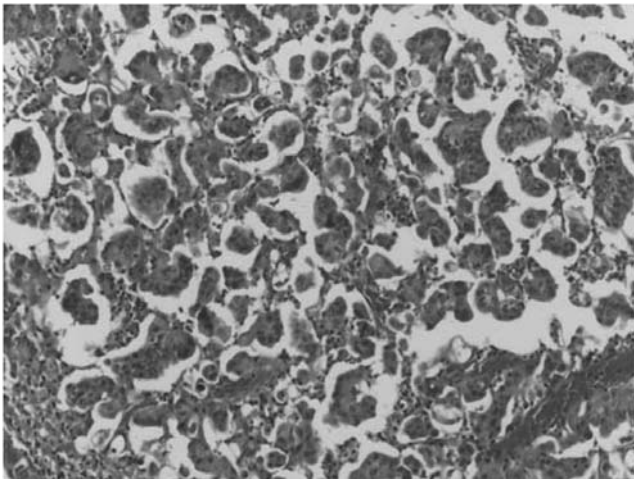

Figure 1. *Papillary serous adenocarcinoma. The tumor exhibits a complex pattern of papillae with cellular budding. Haematoxylin and eosin stain, ×200.*

125 in response to the therapy is indicative of better prognosis (15). The rapid normalisation of CA-125 corresponds with the long progression-free period in our case. We hypothesised that CA-125 might serve as an additional parameter for decision making regarding whether or not to undergo chemotherapy. Persisting or rising CA-125 levels after surgery could indicate the need for chemotherapy, even for patients with disease at an early stage. The most common secondary carcinomas after breast cancer are those of contralateral breast, colon/rectum, corpus uteri, lung, ovary, and skin. The rarest are carcinomas arising from the *cervix uteri*. In statistical terms, having breast cancer is 'protective' against cancer of the uterine cervix (odds ratio=0.35-0.72 for all age groups). The causal relationship for these associations is not well-understood, except that a low socioeconomic status is a risk factor for cervical cancer, while a high socioeconomic status is a risk factor for breast cancer (5). We know little about tamoxifen and non-squamous cervical cancer. The proposed antitumour effect of tamoxifen has not been confirmed; on the other hand, there are no data indicating for a tumour-promoting effect of tamoxifen (16). In our case, the estrogenic effect of tamoxifen could not be attributed to the development of the secondary tumour, because staining for both, ER and PR, was negative. Moreover, tamoxifen is a widely used drug, and to our knowledge, our case is the first report of PSCC after breast cancer.

Conclusion

The management of very rare subtypes of cancer underlines the role of accumulating experience through case reports. Immunohistochemistry plays an important role in the diagnosis of rare tumours. While adjuvant chemotherapy has been established for other serous adenocarcinomas (ovary, endometrium), no definitive recommendation is possible for early-PSCC. The absence of chemotherapy in a case of poorly-differentiated papillary-serous carcinoma with high expression of p53, Ki67 >50%, and elevated serum CA-125 could be considered as hazardous. In the few published cases, the response to platinum-based chemotherapy was good (14). On the other hand, the two largest series with 17 (3) and 12 (4) cases, respectively, indicate that PSCC behaves aggressively when diagnosed at an advanced stage, but the outcomes at stage I are similar to those for patients with adenocarcinoma of the usual type. The uneventful follow-up of more than three years in our case supports this hypothesis.

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