

“Occult” neuroendocrine component and rare metastatic pattern in cervical cancer: Report of a case and brief review of the literature

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Summary

Distant metastases in small cell carcinomas of the uterine cervix are rare, and a disseminated manifestation of the disease is uncommon.

This is a case report of a 40-year-old woman treated with platin-based radio-chemotherapy for a moderately differentiated squamous cell cervical cancer FIGO Stage IB1 (with positive paraaortic lymph nodes). One year later she presented with remarkably unusual cutaneous metastases of the left thumb and scalp as the first signs of spread of disease, including kidney, lung and brain metastases. An advanced retrospective immunohistochemical staining of the cervical biopsy discovered a small neuroendocrine component of the carcinoma as the presumably causative factor for the rare metastatic pattern and poor prognosis.

Key words: Cervical Cancer, squamous cell carcinoma, neuroendocrine carcinoma, thumb metastasis, renal metastases, staging lymphadenectomy.

Introduction

Metastases from squamous cell carcinomas (SCC) of the uterine cervix are uncommon. Most often the tumor extends locally and by lymphatic spread. Hematogenous dissemination usually occurs late in the course of the disease and represents less than 5% of all patients with metastatic cervical cancer. The most common sites are the lung (3-57% [1]), bone (0.8-23%), liver (1.2 to 2.2 % [2]) and brain (0.3% [3]), respectively. The reported incidence of skin metastases ranges from 0.1 to 2% [4]. In contrast, rare neuroendocrine carcinomas (NEC) of the uterine cervix (1-5% of all cervical tumors) are extremely aggressive, mirrored in 80% of relapses within the first year after diagnoses.

The prognosis in Stage IB patients with SCC is determined by tumor dimension, lymph node involvement, lymphovascular involvement, poor differentiation, and certain histological types, such as adeno- and clear cell carcinoma [5]. Survival is more favorable for patients with tumors < 4 cm than for those with tumors > 4 cm (IB2), while an increased rate of nodal metastases is due to the larger tumor size. The risk for paraaortic lymph node metastases in carcinomas of the uterine cervix FIGO Stage IB ranges from 2% to 9% [6]. Prognosis of NEC is poor and up to 60% of early-stage patients show regional lymph node metastases.

While radiochemotherapy alone and radical surgery of SCC have been shown to be equally effective in early stages, in node-positive patients with operable cervical cancer FIGO Stage IB-IIA the postoperative, adjuvant radiochemotherapy undoubtedly causes increased morbidity [7]. Special treatment concepts for NEC, hitherto, have not been established. Another difficulty is the likely underestimated incidence of the synchronous occurrence of SCC or adenocarcinoma and NEC. For the primary pathological assessment, an immunohistochemical staining of SCC or adenocarcinomas is not required.

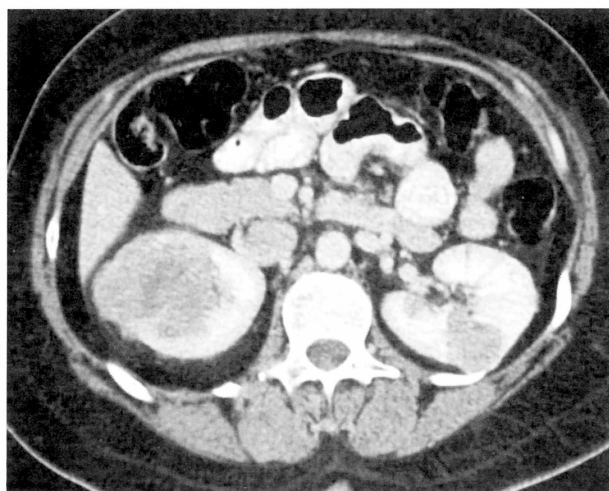


Figure 1. — CT scan of the abdomen showing bilateral renal metastases.

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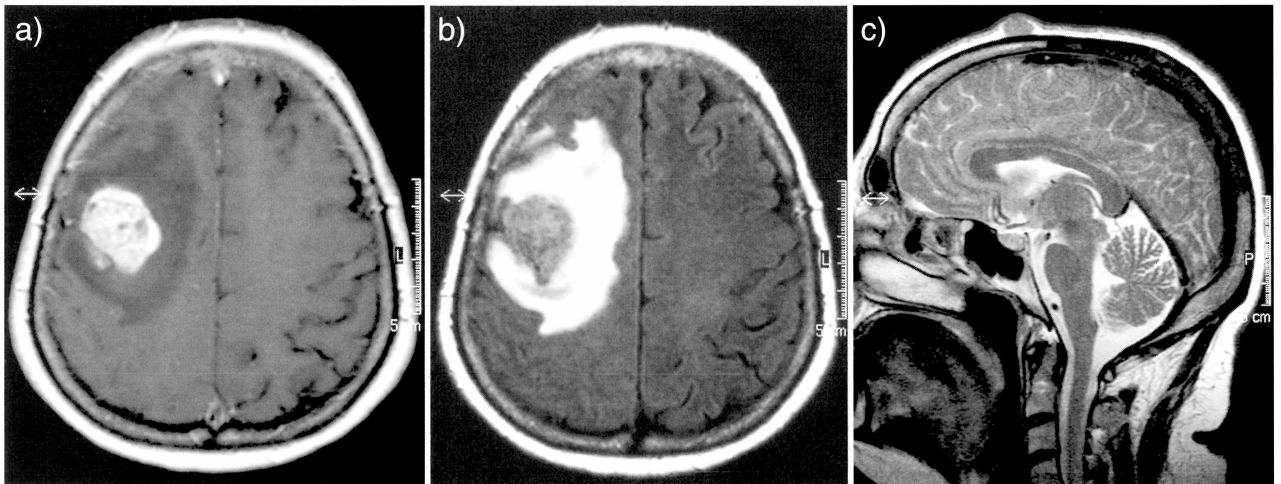


Figure 2. — Magnetic resonance imaging with axial T1-weighted post-contrast sequences a) and flair sequences b) show a large metastasis in the right frontal lobe with surrounding edema. On the sagittal T2-weighted sequence c) an additional subcutaneous metastasis is demonstrated.

An uncommon pattern of metastases involving the left thumb, scalp, lung, kidneys, and brain in a patient with carcinoma of the uterine cervix initially considered as SCC FIGO Stage IB1 after radical radiochemotherapy is reported. However, the retrospective immunohistochemical investigation exhibited a small neuroendocrine fraction of the carcinoma.

Case Report

A 40-year-old Turkish woman was referred to our department with a histologically proven moderately differentiated squamous cell cervical carcinoma FIGO Stage IB1 (3 cm). Staging laparoscopy, preceding the intended laparoscopic-assisted radical vaginal hysterectomy (LAVRH/Schauta-Stoeckel), revealed paraaortic lymph node metastases. After exclusion of distant metastases (liver and lung) the patient was subjected to platinum-based radio-chemotherapy comprising external radiotherapy in a parametral dose of 63 Gy, the pelvis at 55.8 Gy, including the paraaortic field (50.4 Gy) and intracervical brachytherapy in three fractions of 7.5 Gy each. Radiation was combined with a simultaneous cisplatin chemotherapy (40 mg/m²/week) with a cumulative dose of 340 mg/m². The initially elevated tumor marker SCC antigen decreased from 10.9 µg/l to 0.7 µg/l by the end of the therapy. For the next nine months she was followed-up regularly without any evidence of a clinical tumor relapse.

One year after the initial diagnosis she developed a swelling on her right parietal scalp. A biopsy revealed a cutaneous metastasis of the known squamous cell cancer. Further examination raised suspicion of panaritium of the left thumb. X-rays showed involvement of the bone with necrosis prompting amputation of the finger. Histological examination exhibited infiltrating skin metastasis of the squamous cell carcinoma. Subsequent computed tomography (CT) of the lung discovered mediastinal lymph nodes suspicious of metastases as well as pulmonary metastases. The CT scan of both the abdomen and pelvis detected multiple metastases in both kidneys (Figure 1). MRI of the head was also performed showing a brain metastasis (3.0 x 2.0 x 2.5 cm) in the right frontal lobe (Figure 2). On skeletal

scintigraphy there was no evidence of bone metastases. Palliative cranial radiotherapy was initiated. The patient died eight weeks later of progressive disease. A retrospective immunohistochemical staining of the cervical biopsy exhibited a small, synaptophysin-positive neuroendocrine fraction of the carcinoma.

Discussion

Skin metastases in uterine cervical carcinomas involving the distal upper extremities have rarely been reported and predominantly occur in advanced tumor stages or recurrences up to ten years after initial diagnosis of SCC. Scalp metastases have been described in uncommon cases of advanced cervical carcinoma FIGO Stage IIIB. Both sites of metastases are associated with a poor prognosis of the disease. The mean survival of patients with these findings is three months [8].

The present case is unusual in that there was an early disseminated spread of a primarily diagnosed moderately differentiated squamous cervical carcinoma FIGO Stage IB1, not only involving the left thumb, scalp and lung, but also at much less frequently affected sites such as the kidneys and the brain. To the best of our knowledge this combination of distant metastases in cervical cancer has not yet been published. The occurrence of kidney metastases in a carcinoma of the uterine cervix is extraordinarily rare. This is the second report of kidney metastases in a patient with cervical cancer [9].

The retrospective immunohistochemical investigation of the cervical biopsy revealed a synaptophysin-positive neuroendocrine component of the carcinoma, for which early lymphogenic and hematogenous metastases and a consecutive poor prognosis are more common. The incidence of "mixed" carcinomas is unknown because routine immunohistochemical staining of SCC or adenocarcinomas is not mandatory. However, 100% of NECs express at least one neuroendocrine marker such as

neuron-specific enolase, chromogranin A and synaptophysin [10]. Early identification of a “mixed” tumor type could change the therapeutic concept for patients and perhaps improve the prognosis. Some cases of long-term survivors have been reported in patients who were treated aggressively with radical surgery and radiotherapy. Moreover, preoperative chemotherapy could be considered. First, to minimize the tumor to allow complete surgical resection and, second, to administer another chemotherapeutic regimen including VAC (vincristine, doxorubicin and cyclophosphamide) or PE (cisplatin and etoposide) for which improved survival has been shown (Boruta *et al.*, 2001). In conclusion, ideally, a “mixed” carcinoma should be diagnosed earlier, and multicenter randomized controlled trials are warranted to establish alternative treatment options for these patients.

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