Brain metastasis and carcinomatous meningitis from vulvar squamous cell carcinoma: case report

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Summary

Background: Brain metastasis and carcinomatous meningitis from gynecological tumors are an uncommon event, usually related to choriocarcinoma, ovarian and cervical cancer. *Case:* A 74-year-old woman was diagnosed with locally advanced vulvar squamous carcinoma. Initial therapy consisted of multiagent chemotherapy and vulvar, pelvis and groin irradiation. The patient subsequently developed widely spread metastatic disease including brain and meningeal metastases. *Conclusion:* The rising incidence of central nervous system metastasis in the last two decades is probably associated with treatment-related improvement in life expectancy. To our knowledge, this is the first case reported of brain metastases and meningeal carcinomatosis associated with vulvar squamous cell carcinoma.

Key words: Vulvar cancer; Brain metastasis; Meningeal carcinomatosis.

Introduction

Cancer of the vulva is the fourth most common malignancy of the female genital tract. Recent estimates indicate that 3,870 of the 79,480 annual cases of female genital cancer arise in the vulva, representing approximately 4.8% of the total cases. Currently, about 80% of vulvar carcinomas are curable, making vulvar carcinoma responsible for approximately 800 deaths annually in the United States [1]. Invasive vulvar cancers typically metastasize by embolization through the lymphatic system to the regional lymph nodes, and by direct extension to adjacent structures (vagina, urethra, clitoris and anus). Hematogenous dissemination, which typically occurs late in the course of the disease, is rare in patients without inguinofemoral lymph node involvement [2].

We report the case of a patient who presented with brain metastasis and meningeal carcinomatosis as a final event of a vulvar cancer. To our knowledge, this is the first case reported of central nervous system dissemination of a squamous cell vulvar cancer.

Case Report

A 74-year-old woman presented in March 2003 with a 3-month history of pruritus and vulvar pain. Physical examination showed an ulceroproliferative growth in the right pudendal labium, upper third of the left labium majora, the clitoris and the upper half of the vagina. A biopsy of the lesion demonstrated a poorly differentiated squamous cell carcinoma. A chest X-ray and abdominal-pelvic computed tomography (CT) scan did not show distant metastasis. The patient was diagnosed with squamous cell carcinoma of the vulva, Stage III (T3, N0, M0) of the UICC staging system and referred to the Oncology Department. External radiation therapy was administered using AP-PA fields to the vulva, lower pelvis and bilateral inguinal lymph nodes to a total dose of 45 Gy and brachytherapy boost to deliver an additional 20 Gy. Concomitant chemotherapy was administered during radiotherapy treatment. The chemotherapy schedule consisted of 50 mg/m of cisplatin on day 1 and 1000 mg/m^2/24h of 5-fluorouracil as continuous infusion on days 1-4 during the first and last weeks of radiation, according to the guidelines published by Cunningham *et al.* [3]. The scheduled second course of chemotherapy was not administered due to grade 3 diarrhea. The treatment was completed in August 2003, and physical and pelvic examination showed complete response.

Three months later local recurrence and distant metastases were observed. A CT scan demonstrated bilateral lung metastases and a bone scan showed metastasis to the spinal column, skull, sternoclavicular joint and right femoral head. The patient received three courses of 3-weekly paclitaxel of 175 mg/m^2 over 3-hour infusions without response. In February 2004, she presented with a history of dizziness, lethargy, nausea and vomiting. Neurological examination revealed hypoesthesia and paresis in the right upper extremity. Cranial CT showed a 1 x 1 cm ring-enhancing lesion in the left precentral gyrus associated with brain edema which was diagnosed by the neuroradiologists as brain metastases. T2-weighted magnetic resonance imaging (MRI) confirmed this finding in addition to diffuse, thick, partially nodular enhancement of the dura mater and enhancement of the subarachnoid space in cerebral sulci suggesting meningeal carcinomatosis (Figures 1 and 2). Lumbar puncture showed an increased cerebrospinal fluid (CSF) protein level, but the cytological exam was negative for malignant cells.

Due to the findings on MRI, therapy with dexamethasone was initiated, but during the following days, the patient's neurological dysfunction worsened, her performance status declined rapidly and she progressed to coma. Due to her poor medical condition, radiation therapy was not prescribed, and the patient died in March 2004.

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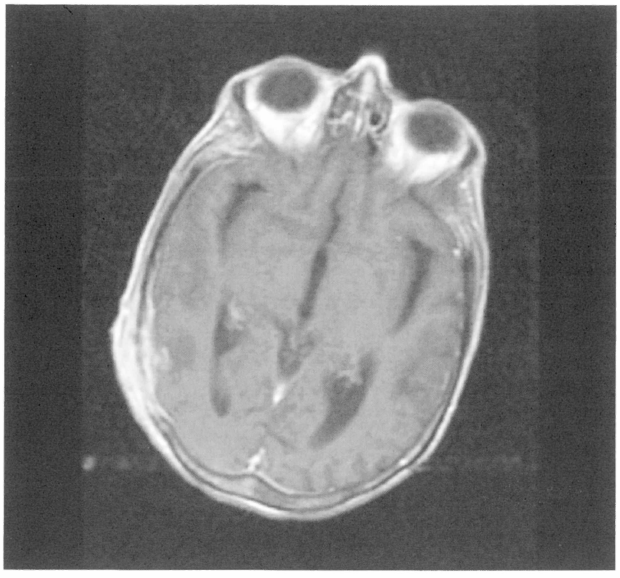

Figure 1. — Transversal view of MRI showing diffuse meningeal enhancement.

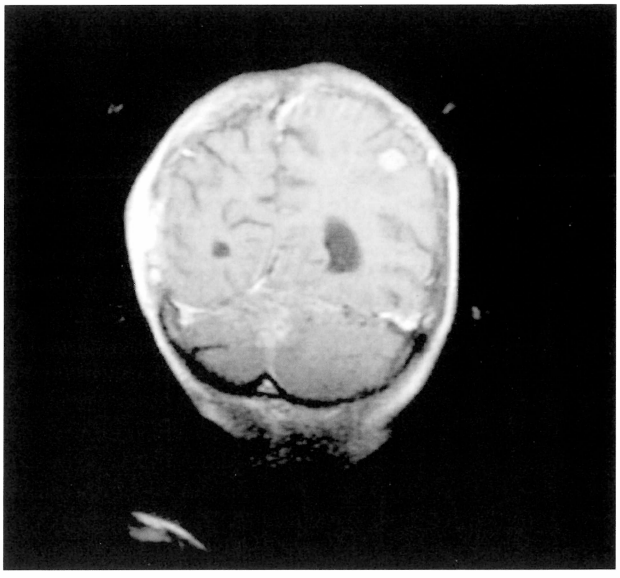

Figure 2. — Coronal view of MRI showing left precentral gyrus metastases.

Discussion

Brain metastasis and carcinomatous meningitis from gynecological tumors are uncommon except for choriocarcinoma, which is reported to metastasize to the central nervous system in up to 40% of the cases. The majority of cases reported are associated to ovarian, cervical and endometrial cancer. Despite the low incidence of central nervous system metastasis from gynecological tumors, it seems to have increased over the past decade, and may be the paradoxical result of the effectiveness of drugs that do not cross the blood-brain barrier. As a result of the increased survival in patients receiving chemotherapy, brain metastases may become symptomatic [4].

In this case, our patient presented with locally advanced squamous cell carcinoma. The standard treatment for advanced carcinoma of the vulva has been enbloc resection of the primary tumor and regional lymph nodes. However, in view of the high morbidity of these procedures, other treatment modalities are often employed. Preoperative chemoradiation may allow downstaging of the tumor, allowing a more conservative surgical resection, and even be curative in some cases. Two series that administered cisplatin and 5-fluorouracil during the first and last weeks of radiotherapy to women with advanced disease achieved complete clinical response rates of 64% and 67%, respectively [3, 5]. The role of subsequent surgery is unclear. In the first study, there was only one recurrence of the nine women with a complete clinical response, despite the fact that surgery was not performed. In our patient, although complete clinical response was obtained, local and distant recurrence appeared three months after treatment. For advanced recurent disease, no standard treatment has been established and long-term survival is extremely rare. The literature supports the use of 5-fluorouracil or cisplatin as single agents or in combination to have sensitivity against squamous cell vulvar cancer [6]. There are few studies suggesting improvement in 5-year survival, thus these patients may benefit from recruitment into research protocols.

Although vulvar cancer metastasizes most often through the lymphatic system, hematogenous spread can occur in association with bulky disease, poorly differenciated tumors and lymph node metastases [6]. The lungs and bone are the most frequent sites of distant metastases associated with vulvar cancer. To our knowledge, no previous cases of brain metastasis and meningeal carcinomatosis related to squamous vulvar cancer have been described. The other two cases of brain metastasis from vulvar cancer reported were a Bartholin's gland carcinoma [7] and a vulvar adenocarcinoma associated with Paget's disease [8].

Clinical presentations of meningeal carcinomatosis include headaches, focal neurological deficits, radiculopathies, sensory abnormalities, and encephalopathy. The single most useful diagnostic test for meningeal carcinomatosis is the demonstration of malignant cells on examination of the cytology of spinal fluid (CSF). This is usually obtained by lumbar puncture, but it may be necessary to perform repeated sample examination before malignant cells are seen. Concentration of protein or glucose and number of cells may vary at different levels of the neuraxis, thus emphasizing the multifocal nature of meningeal carcinomatosis [9]. In view of the fact that cytological examination may remain negative in some patients despite repeated CSF testing, some investigators have advocated neuroimaging as an additional tool to assess meningeal carcinomatosis. Freilich

et al. suggested that the presence of typical clinical features along with appropriate neuroimaging abnormalities should be adequate to make a diagnosis, even in the absence of positive CSF cytology [10]. A variety of neuroradiographic methods are available to investigate patients with suspected meningeal carcinomatosis. Gadolinium-enhanced MRI is the most sensitive and least invasive neuroradiological imaging tool available to detect meningeal carcinomatosis [10]. According to the gadolinium-enhanced MRI (Gd-MRI), meningeal carcinomatosis may be classified into four groups: group 1 includes pure leptomeningeal carcinomatosis, group 2 dural carcinomatosis, group 3 spinal leptomeningeal carcinomatosis and group 4 normal Gd-MRI except for hydrocephalus [11].

The prognosis of carcinomatous meningitis is poor, with a median survival of four to six weeks if left untreated and two to three months with therapy [12]. Treatment options include radiation therapy, intrathecal chemotherapy, or systemic chemotherapy. Radiotherapy is used for palliation of symptoms and to decrease bulky disease such as coexistent parenchymal metastases [13]. Intrathecal chemotherapy options include methotrexate, thiotepa and ara-C. Retrospective analysis or comparison to historical studies suggests that the administration of chemotherapy to the cerebrospinal fluid improves the outcome of patients with neoplastic meningitis [14]. Systemic administration of chemotherapy agents with high cerebrospinal fluid penetration, such as high-dose methotrexate may be a treatment option. However, not all patients with meningeal carcinomatosis are candidates for these aggressive treatments. Most authors agree that they should be offered to patients with a life expectancy greater than three months and a Karnofsky performance status greater than 60%, no fixed neurological deficits, minimal systemic disease and reasonable systemic treatment options if needed [15]. In our case, neurologic dysfunction progressed and the patient died in a few days.

In conclusion, although carcinomatous meningitis is a rare event in advanced vulvar cancer, this diagnosis should be considered in patients with neurological symptoms or signs not explained by other medical reasons.

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