Meningeal carcinomatosis as a late complication of brain metastases of epithelial ovarian carcinoma

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Summary

The brain represents a rare site of metastasis in patients with epithelial ovarian carcinoma (EOC). In recent decades there has been an apparent increase in the number of EOC patients diagnosed with brain metastases, probably as a result of improved prognosis of patients with advanced tumors, but cases of meningeal carcinomatosis complicating EOC remain rare. A patient with Stage III EOC had brain metastases diagnosed 31 months after primary surgery. The isolated brain metastases were controlled with radiosurgery, surgery and chemotherapy. Forty-five months after the diagnosis of brain metastases, meningeal carcinomatosis was diagnosed which led, despite intrathecal therapy, to a fatal outcome. At autopsy, the disease was limited to the central nervous system. Meningeal carcinomatosis may represent a late fatal complication of brain metastases of EOC.

Key words: Brain metastasis; Epithelial ovarian carcinoma; Meningeal carcinomatosis.

Introduction

The survival of patients with epithelial ovarian carcinoma (EOC) has improved substantially in recent decades. The peritoneal cavity represents the most common site of metastatic spread in EOC, and in advanced EOC the disease is frequently limited to the peritoneum. However, the marked prolongation of survival resulting from multimodality treatment is changing the natural history of EOC, and more patients live long enough to develop distant metastases. Among sites of distant relapse, central nervous system (CNS) metastases, once considered very rare, are now being diagnosed with increasing frequency. In hospital population series, estimates of the frequency of CNS metastases in EOC range between 0.5 and 12 %. The frequency of CNS metastases in EOC has increased since the 1970s, and this increase is thought to reflect a change in the clinical course of the disease resulting from the introduction of more effective local and systemic therapy [1]. In most cases of EOC, CNS metastasis of brain parenchyma is involved, but metastatic spread to the meninges is rather exceptional.

We present a case of an EOC patient with metachronous brain metastases that were controlled with radiosurgery, surgery and chemotherapy for 45 months, but were later complicated by fatal meningeal carcinomatosis.

Case Report

A 48-year-old woman presented with Stage III serous EOC treated by bilateral salpingo-oophorectomy, hysterectomy and debulking surgery in February 1998. After the surgery, four courses of the systemic combination of paclitaxel (135 mg/m^2 24-hr infusion) and cisplatin (75 mg/m^2) were administered. Subsequently, an intraperitoneal catheter with subcutaneous port system was implanted, and the patient received another three courses of paclitaxel and cisplatin intraperitoneally. Serum CA125 levels normalized and the patient subsequently received three courses of intraperitoneal cisplatin with systemic cyclophoshamide and four courses of intraperitoneal carboplatin and etoposide. Six courses of intraperitoneal interferon-γ and interleukin-2 were then administered as consolidation therapy. Treatment was completed in 1999, and complete clinical remission was achieved.

In September 2000 the patient presented with generalized tonic seizures and light paresis of the left upper extremity and left facial nerve. A right frontal mass (18 x 14 x 13 mm) and a small metastasis in the gyrus cinguli (3 mm) were detected by magnetic resonance imaging (MRI), and the patient was treated with radiosurgery in October 2000. Both brain metastases in the right frontal region and right gyrus cinguli were irradiated using the gamma knife in a single session with minimal dose (D min) to the periphery of 21 Gy on 50% isodose curve. The patient was subsequently well under prophylactic therapy with sodium valproate and was able to return to her work as a nurse. In September 2002 the patient had repeated generalized tonic seizures. Progression of metastasis in the frontal lobe was detected by MRI. Biopsy confirmed EOC metastasis, and a complete resection of the brain metastasis was performed in December 2002. The patient was subsequently treated with a combination regimen including 5-fluorouracil, gemcitabine and cisplatin [1]. Between January and May 2003 the patient received four cycles of this combination regimen. She was asymptomatic until March 2004 when she complained about headaches and reported seizures. Control MRI revealed two lesions located in the right frontal lobe. These lesions were retreated by radiosurgery in April 2004 with single D min 19 Gy on 50% isodose curve. Subsequently, chemotherapy with the combination of 5-fluorouracil, gemcitabine and cisplatin was reinstituted. Three cycles of this regimen were administered, but the condition of the patient deteriorated. The patient complained about instability, impaired movement of the lower extremities, and falls. Cog-

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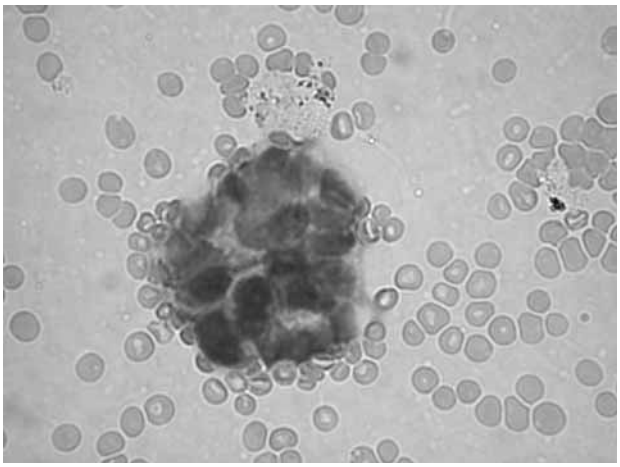

Figure 1. — Malignant cells in cerebrospinal fluid (May-Grünwald-Giemsa, magnification 400 x).

nitive impairment was also evident. Control MRI in June 2004, 45 months after the initial diagnosis of brain metastases, revealed regression of the metastasis in the right frontal lobe.

Because of the conflict between radiologic improvement and neurological deterioration, the diagnosis of meningeal carcinomatosis was suspected, and spinal fluid was obtained for cytological analysis. Cytological examination confirmed the presence of tumor cells (Figure 1). As – apart from the brain metastases that were controlled by radiosurgery – the metastatic involvement of the meninges was isolated, an Ommaya reservoir was implanted for intrathecal therapy. By that time, left hemiparesis manifested and cognitive functions further deteriorated. Before the start of therapy cerebrospinal fluid CA125 concentrations were increased compared to serum (Figure 2). Methotrexate (20 mg) was administered intrathecally on June 17, 2004, and five doses of the combination of methotrexate (15 mg), cytarabine (50 mg) and hydrocortisone (15-30 mg) were administered between July 1 and July 13. The intrathecal application of combination of methotrexate and cytarabine resulted in a decrease of serum and cerebrospinal fluid CA125 concentrations, but clinically the condition of the

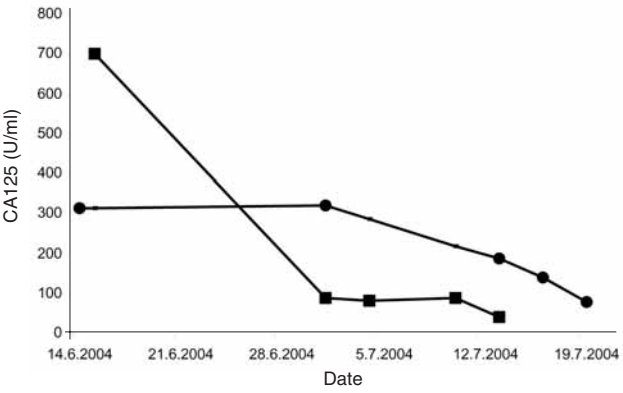

Figure 2. — Cerebrospinal fluid and serum CA125 concentrations. Serum CA125 was determined during intratheracal chemotherapy in cerebrospinal fluid (squares) and serum (circles) by immunoradiometric assay using a commercial kit (Immunotech, Marseille, France) according to the manufacturer's instructions.

patient further deteriorated. She was unable to sustain active movement, confined to bed and somnolent. Moreover, the administration of intrathecal therapy was later complicated by leukopenia, thrombocytopenia and gastrointestinal toxicity (diarrhea). Leucovorin was administered, and antibiotic therapy was initiated. The final course was complicated with pneumonia which did not respond to antibiotic therapy. The patient died on July 21, 2004. Autopsy revealed isolated metastatic involvement of the CNS with carcinomatosis involving most of the meningeal surface of the brain and spinal cord, recurrent metastasis in the right frontal lobe, bilateral pneumonia and deep vein thrombosis with pulmonary embolism that did not seem to be hemodynamically significant.

Discussion

Meningeal metastases in the present patient developed late in the course of CNS metastases, as an apparent sequel to brain metastases that were controlled for more than three years with radiosurgery, surgery and systemic chemotherapy. The survival of our patient was remarkably long compared to survival of most other patients with EOC brain metastases reported in the literature. It is evident that the increased frequency of CNS metastases in EOC is linked with the advent of effective therapy, resulting in significant prolongation of survival that allows for the manifestation of distant metastases. Similarly, it is possible that metastatic involvement of the meninges was associated with long survival after diagnosis of brain metastasis in our patient. We have recently observed meningeal metastases in another EOC patient who survived more than three years after diagnosis of brain metastases [1]. Another factor that could be linked to metastatic spread to the meninges could be brain surgery which was performed during the course of the disease in both of these patients [2].

CNS metastases are still a rare complication in patients with EOC, and cases of meningeal carcinomatosis are even more exceptional. EOC also represents an unusual primary among patients with CNS metastases. The brain is by far the most common site of CNS metastases in EOC, and more than 200 cases of EOC brain metastases have been reported [1]. We have recently performed a pooled analysis of the survival of patients with EOC brain metastases reported in the literature. The most favorable outcome was observed in patients treated by surgery combined with radiotherapy and/or chemotherapy, and median survival of patients treated by combined modality therapy was more than one year [1]. Although the prognosis of brain metastases is, in general, rather unfavorable with median survival between three and four months, patients with solitary brain metastasis or a chemosensitive primary, e.g. breast carcinoma or EOC, have a more favorable prognosis [3]. In the largest series of patients with EOC brain metastases, the median survival was six months [4].

In contrast, fewer than 20 cases of meningeal carcinomatosis in EOC patients have been reported so far [5, 6]. The published reports focused on patients with isolated meningeal carcinomatosis, and little has been published

so far about meningeal carcinomatosis as a late complication of parenchymal brain metastases. In our patient, signs of meningeal carcinomatosis were not obvious on MRI, and the diagnosis was established by cytological examination of cerebrospinal fluid. The cerebrospinal fluid CA125 concentration was increased compared to serum. There are only anecdotal data on the use of cerebrospinal fluid CA125 measurement in EOC meningeal carcinomatosis [5], but the present observation suggests, in agreement with previous reports, that increased cerebrospinal fluid CA125 (compared to serum) concentrations may be helpful in establishing the diagnosis. Both cerebrospinal fluid and serum CA125 levels decreased after intrathecal chemotherapy. However, in contrast to a recent report on patients with breast carcinoma and meningeal carcinomatosis [7], the decrease in tumor marker concentrations was not accompanied by clinical improvement. Our patient had clinical signs of carcinomatous encephalopathy that progressed in spite of an apparent response detected by serial CA125 measurements. Terminal pneumonia was also considered a consequence of progressive carcinomatous encephalopathy. The present experience indicates that tumor cell destruction in patients with extensive meningeal carcinomatosis may not lead to functional improvement. Inflammatory phenomena accompanying tumor cell destruction could also explain the neurological deterioration. It is therefore likely that some cases of carcinomatosis involving most of the meningeal surface may be refractory to any currently available therapy. In fact, similarly to the present case, most patients with EOC meningeal metastases have died within one month of presentation [8-10], although individual cases of patients with longer survival after therapy have also been reported [5, 6], including patients treated with intrathecal chemotherapy. Among 13 cases reviewed by Khalil *et al*. [5], seven patients died within one month of diagnosis of meningeal metastases.

In conclusion, meningeal carcinomatosis may represent a late fatal complication of brain metastases of EOC. It is possible that with the improvement in management of EOC patients, including the patients with brain metastases, the diagnosis of meningeal carcinomatosis will be more frequent.

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