

Primary Undifferentiated Ovarian Carcinoma Diagnosed by its Metastasis to Brain: An Unusual Case Report

Intrakranial Metastaz ile Tanı Konmuş Primer İndiferansiye Over Karsinomu: Olgu Sunumu

ABSTRACT

OBJECTIVES: Intracranial metastasis of ovarian tumours is rarely seen with an incidence 0.1-5% but simultaneous diagnosis of primary undifferentiated carcinoma of the ovary and its CNS metastasis has not been published previously.

MATERIAL and METHODS: A 56-year-old woman presented with headache and visual disturbance. She underwent cranial MRI and abdominal ultrasound.

RESULTS: On examination, a bilateral right homonymous hemianopia and left papilledema were found. Cranial MR showed multiple ring-enhancing intracranial tumours. A right ovarian mass measuring 100x85x135 mm was discovered with abdominal ultrasound. She underwent extensive gynecological surgery. The histopathological diagnosis was undifferentiated ovarian carcinoma which dedifferentiated from endometrioid-type ovarian adenocarcinoma. A week after gynecologic surgery, the patient underwent surgery for a left occipital tumour which proved to be anaplastic carcinoma metastasis. The patient succumbed 15 months after the diagnosis.

CONCLUSIONS: Although metastasis from undifferentiated ovarian carcinomas to the central nervous system have been published with the CNS disease often developing long after the initial diagnosis of primary tumour; simultaneous diagnosis of primary undifferentiated carcinoma of the ovary and its CNS metastasis as described in our case may rarely occur.

KEY WORDS: Epithelial ovarian adenocarcinoma, Central nervous system, Metastasis, Immunohistopathology, Undifferentiated ovarian carcinoma, Ovarian cancers

ÖZ

GİRİŞ: Epitelyal over tümörleri (EOT) diğer over tümörlerine göre daha sık görülmekte olup en fazla seröz alt tipte olmaktadır. EOT, %0,1-5 oranda intrakranial metastaz yapar ancak primer indiferansiye over karsinomu ile eş zamanlı onun intrakranial metastazı tanısı konmuş olgu bildirimini daha önce literatürde rastlanmamıştır.

MATERYAL ve METOD: 56 yaşındaki kadın hasta başağrısı ve görmede azalma rahatsızlığı ile başvurdu. Hastaya beyin manyetik rezonans ve abdominal ultrasonografi görüntülemeleri yapıldı.

SONUÇ: Muayenede bilateral sağ hemianopsi ve sol papil ödemi saptandı. Beyin manyetik rezonans görüntülemesinde çok sayıda etrafı kontrast tutan tümörler görüldü. Metastaz taramasına yönelik yapılan abdominal ultrasonografide sağ over yerleşimli 100x85x135 mm boyutlarda tümör tespit edildi ve cerrahi rezeksiyon sonrası immünohistopatolojik incelemede, tümörün endometrioid tip over adenokarsinomundan dediferansiye olmuş indiferansiye over karsinomu olduğu saptandı. Bir hafta sonra sağ oksipital yerleşimli en büyük metastatik kitle eksize edildi ve patolojik inceleme sonucu anaplastik karsinom saptandı.

TARTIŞMA: İndiferansiye over karsinomlarının intrakranial metastazı, genelde hastalığın tanısının konulmasını takip eden geç dönemlerde olmasına rağmen bizim olgumuzdakine benzer şekilde eş zamanlı primer over tümörü ve onun intrakranial metastazı tanısı da mümkün olabilmektedir.

ANAHTAR SÖZCÜKLER: Epitelyal over adenokarsinomu, Santral sinir sistemi, Metastaz, İmmunohistopatoloji, İndiferansiye over karsinomu, Over kanserleri

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INTRODUCTION

Ovarian carcinomas have higher morbidity and mortality rates than other gynecological malignancies (7, 20). Epithelial ovarian carcinomas (EOCs), which are the most common type of ovarian tumours, are known to metastasize to other organs at the time of initial diagnosis of the ovarian mass (6). Intracranial metastasis is rarely seen with an incidence 0.1-5 % and occurs usually as a late manifestation of the disease (3, 20). In autopsy series, this incidence rises to 1-6 % (11, 15, 20). Metastasis from undifferentiated ovarian carcinomas to the central nervous system (CNS) has been reported with the CNS disease often developing long after the initial diagnosis of primary tumour. Simultaneous diagnosis of primary undifferentiated carcinoma of the ovary and its CNS metastasis has not been published previously.

CASE REPORT

A 56-year-old woman who had a history of migraine since her middle ages presented with headache and visual disturbance. She had two children and smoked 30 cigarettes a day. On examination she had bilateral right homonymous hemianopia and left papilledema. Magnetic resonance imaging (MRI) showed a left occipital cystic-necrotic tumour which measured 40x50x50 mm together with multiple millimetric intracranial contrast-enhancing lesions (Figure 1).

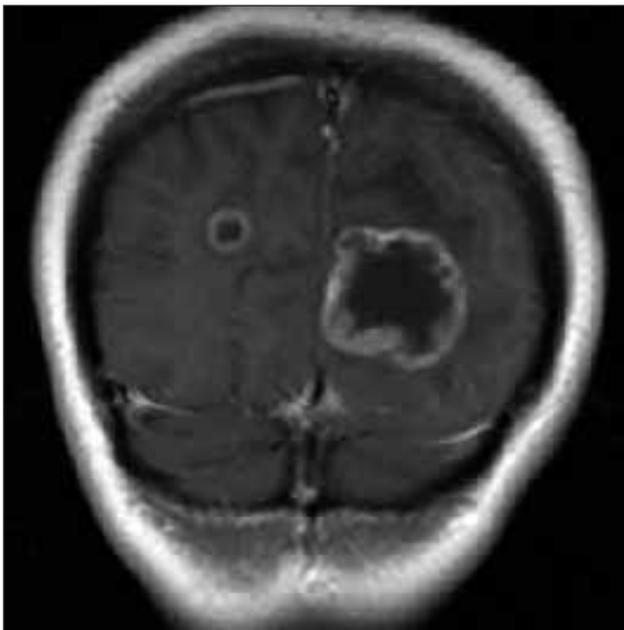


Figure 1: Coronal T1 weighted MRI with contrast show the metastatic lesion of cerebrum before the surgery.

Serum levels of CA19-9, CA125 and CEA were all higher than the upper limit of normal. Initial clinical impression was lung cancer metastasis. Her thorax computed tomography (CT) showed multiple perihilar enlarged lymph nodes without a parenchymal mass. A right ovarian mass measuring 100x85x135 mm and multiple parailiac lymph nodes without pelvic or intraabdominal organ metastases were discovered at abdominal ultrasound (US). Scintigraphy with 20 mCi 99m Tc-MDP was negative for bone metastasis. All results suggested that the cranial metastatic lesions most probably originated from the ovarian mass. Extensive radical surgery consisting of total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy, parailiac and periaortic lymphadenectomy was performed by a gynecological surgeon. Histopathological diagnosis was undifferentiated ovarian carcinoma with cystic-necrotic and high grade mitotic areas without glandular formation. The uterine cervical PAP smear and intraabdominal wash-out cytological specimens taken intraoperatively contained no malignant cells. Other genital organs and omentum were not invaded with neoplastic cells but few paraaortic lymph nodes stained positive for cancer cells (FIGO grade II and surgical stage IV). At immunohistochemical (IHC) analysis, the tumour cells reacted strongly with epithelial membrane antigen (EMA) and pancytokeratin (panCK), and reacted focally with vimentin. Immunostaining for CD56 and chromogranin was negative. IHC suggested that the tumour originated from an endometrioid-type ovarian adenocarcinoma.

One week after gynecological surgery she was operated for a left occipital tumour. The histopathological diagnosis was anaplastic carcinoma (Figure 2). Cytological examination of the cerebrospinal fluid was negative. She was discharged with a Karnofsky performance score of 90/90.

Radiation therapy (30 Gy to the cranium and 15 Gy to the abdomen) and chemotherapy (carboplatine combined with paclitaxel 6 cycles in total) were considered postoperatively. Over the following 8 months, her vision decreased bilaterally to nearly blindness and neuroophthalmological examination suggested radiation neuritis as the main reason. Brain MR images taken 14 months after cranial surgery showed multiple new cerebral and cerebellar metastases (Figure 3).

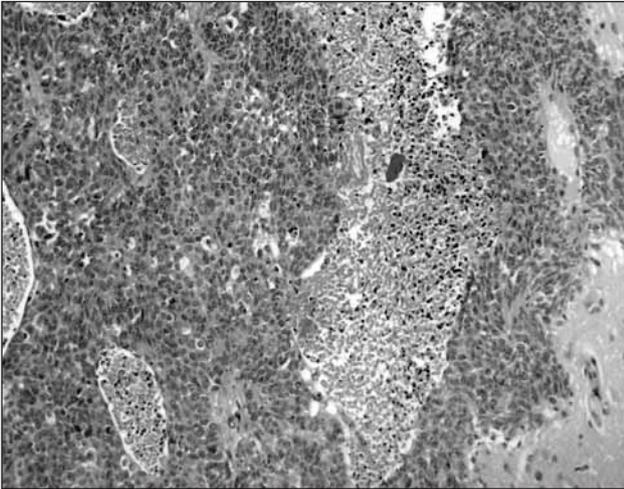


Figure 2: Anaplastic carcinoma metastasis to brain with foci of necrosis. Atypical epithelial cells with eosinophilic cytoplasm and round to oval nuclei grow in a solid fashion. Frequent mitoses are observed (HE stain, original magnification is x100).

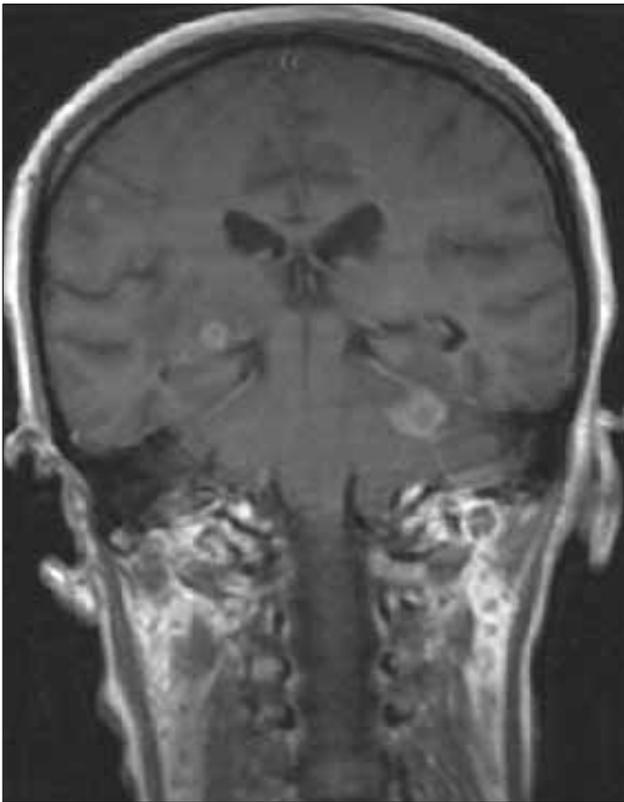


Figure 3: Coronal T1-weighted MRI with contrast shows the new metastatic lesions of the cerebrum and cerebellum of the patient who was at the end stage.

Simultaneous abdominal US showed multiple organ metastasis including the liver, bilateral kidney, right surrenal gland and the right abdominal skin. The right paramedian metastatic mass to the abdominal skin was tender and painful and had to

be removed and the histopathological picture was the same (Figure 4). The patient succumbed 15 months after the initial diagnosis.

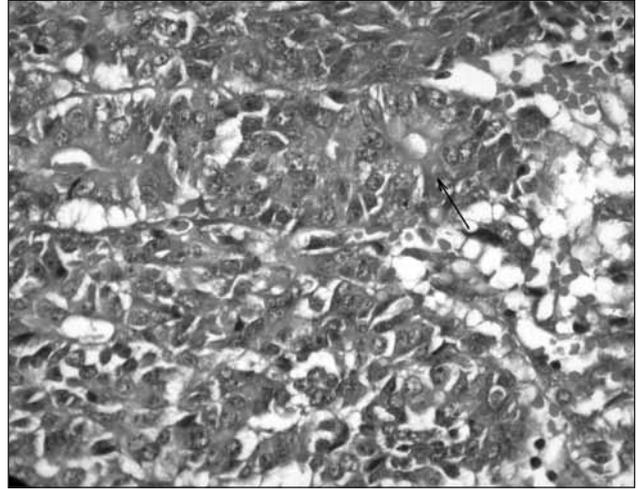


Figure 4: Rare glandular formations are observed in skin metastasis (HE stain, original magnification is x400).

DISCUSSION

EOCs are classified as serous, endometrioid, mucinous, clear cell, transitional, mixed and undifferentiated subtypes. The histological grade of EOC is decided by the cell architecture, nuclear pleomorphism and mitotic activity (10, 21). Immunohistochemically EOCs react positively with epithelial membrane antigen (EMA), inhibin, pancytokeratin (panCK), and calretinin and in this way differ from sex-cord stromal tumours (4, 22). The endometrioid subtype reacts strongly with EMA and panCK as compared to the other types (17, 21, 23). Endometrioid adenocarcinomas developing in the endometrium and ovary most often stain strongly for vimentin, which greatly aids in distinguishing them from endometrioid or pseudoendometrioid tumours arising from the endocervix, colon or lung (8). Our patient's tumour cells strongly reacted with epithelial membrane antigen (EMA) and pancytokeratin (panCK), and focally reacted with vimentin; and we can clearly say that this tumour originated from the ovary.

Some recent studies suggested that endometrioid adenocarcinoma admixed with serous, clear cell features may behave more aggressively than endometrioid adenocarcinoma without these features. Silva et al speculated that the endometrioid type EOC may become dedifferentiated into undifferentiated carcinoma in which the solid

component of the tumour includes neoplastic cells with variable histological appearance, without developing glandular differentiation. These authors further suggested that the neoplasm behaves in a more aggressive fashion when the dedifferentiation starts (23). Glandular formation was not seen in any pathological specimen of our patient except the skin metastases, and the IHC results of her primary tumour suggest that this tumour may have originated or dedifferentiated from the endometrioid subtype with very aggressive clinical and pathological behavior. On the other hand, despite Silva et al's conclusions, the skin metastases of our patient, which were different from ovarian or cerebral lesions with generous glandular formation, support the idea that dedifferentiated endometrioid-type ovarian tumours could eventually produce some glandular formations. In the literature, this dedifferentiation issue is still not settled yet and appears to be very important for the development of new and effective treatment regimens. In our patient, the fact that the tumour did not extend to other organs except the local lymph nodes and the brain tissue, further supports the idea that dedifferentiated ovarian cancers behave very aggressively.

The craniospinal venous system (CSVS) named as Batson's plexus consists of veins, sinuses and venous plexuses. This system communicates with the veins around the spinal column, the segmental veins of the thoracoabdominal wall, pelvic organ plexuses and the azygous system of veins. Because the veins within the CSVS are valveless, the blood circulation is bidirectional, and it may serve as a route for the rostral metastatic spread of the tumour, infection or emboli from pelvic organs (19). Ovarian cancers often spread by direct extension, exfoliation of cells into the peritoneal cavity (seeding), lymphatic dissemination to the pelvis and around the aorta, and less commonly spread hematogenously to distant organs. Although it is not clear how ovarian tumour cells disseminate into the brain parenchyma (12), the lack of spread into the pelvic, intraabdominal or thoracic organs except for local lymph node metastases in our patient suggests that the brain metastases probably occurred by dissemination of tumour cells hematogenously through the Batson's plexus.

Radiation-induced optic neuropathy (RION) which more often becomes manifest after a latency

of three months to a few years is a devastating late complication of radiotherapy to the visual pathways resulting in irreversible uni- or bilateral visual loss (9). Delayed responses to radiation therapy are divided into two types: "early" responses which are characterised mostly by inflammation occur within several weeks and may be reversible, whereas "late" responses which are characterised by vasculitis and necrosis are generally irreversible. There has been no acceptable treatment regimen yet; most of the regimens such as systemic corticosteroids, anticoagulation and hyperbaric oxygen are generally unsuccessful. The authors suggest that hyperfractionation of the radiotherapy may reduce the risk of experiencing this complication (2, 9, 14, 24). Eight months after the cranial surgery, our patient presented with acute progressive visual loss. There was no papilledema or optic atrophy funduscopically and on follow-up MRI there was no compression of the optic nerve and chiasm by any tumour. There also was no enhancement of the optic nerves and optic pathways. Neuroophthalmological examination suggested radiation neuritis as the main reason. She did not benefit from systemic corticosteroids and lost her vision almost totally in one month.

Survival of serous ovarian adenocarcinoma has been reported to be better than other epithelial subtypes, and patients who have isolated CNS metastases from the ovarian neoplasm have better prognosis than other organ metastases (13). CNS involvement of undifferentiated ovarian carcinoma becomes clinically apparent approximately 30 months after the diagnosis of the primary disease (3). There are a few case reports of simultaneous diagnosis of ovarian carcinoma and its CNS metastasis but all these case reports mention primary epithelial ovarian tumours and not undifferentiated ovarian carcinoma (1, 13, 16). Median survival after the diagnosis of CNS metastases is 7.2 months (ranging from 2 to 76 months). The overall survival is higher for patients treated with the surgery-radiotherapy-chemotherapy combination. The prognosis is extremely poor for patients treated with supportive care only (median survival 1.5 months) (13, 18). Skin involvement is a late complication that occurs rarely in ovarian cancer patients. The prognosis after skin metastases is extremely poor (5). Skin involvement of carcinoma in our patient first appeared 10 months after gynecological surgery and

the pathology examination showed glandular formations of the neoplastic epithelial cells which were clearly different from brain metastasis. Multiple organ invasion occurred after surgical resection of the ovarian tumour and the largest CNS metastases despite treatment with radiation and chemotherapy and the patient died with multiorgan failure 15 months after the initial diagnosis.

CONCLUSION

Although metastasis from undifferentiated ovarian carcinomas to the central nervous system has been published often with CNS disease developing long after the initial diagnosis of primary tumour; simultaneous diagnosis of primary undifferentiated carcinoma of the ovary and its CNS metastasis as described here may rarely occur. Finally, we suggest that the possibility of ovarian origin should seriously be considered if a metastatic tumour is found in a female patient's brain as these tumours are still extremely lethal and surgery plus radio- and chemotherapy may only prolong the expected life approximately one year.

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