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Slow Progression of Calcified Cerebellar Metastasis From Ovarian Cancer: A Case Report and Review of the Literature

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Abstract

The report describes a rare case of a patient with a calcified cerebellar metastasis arising from a primary ovarian cancer. The patient was a 33-year-old woman with a long history of stage IIIc ovarian cancer who had undergone transabdominal hysterectomy and bilateral oophorectomy followed by chemotherapy with gemcitabine hydrochloride. Incidentally, computed tomography (CT) revealed a cerebellar tumor with calcification. The size of the tumor gradually increased, and lateral suboccipital craniotomy was performed for gross total removal of the tumor. The histological diagnosis was ovarian mucinous adenocarcinoma. The patient's postoperative course was uneventful, and she was discharged two days after surgery. Brain metastases from ovarian cancer are rare. In the review of metastatic brain tumors arising from a primary ovarian cancer in the Department of Obstetrics and Gynecology at our institution, this phenomenon was noted in only 10 cases (0.24%) of 4,158 patients with ovarian cancer seen at our center over a period of 8 years. Moreover, only three cases of calcified metastatic brain tumor have been reported previously. In conclusion, complete tumor resection may be an acceptable approach for patients with calcified metastatic tumors both for therapeutic considerations and to obtain tissue for confirmation of histopathological diagnosis. Metastatic brain tumors can be calcified, and should be considered within the differential diagnosis of calcified intracranial lesions to avoid any delay in diagnosis or treatment.

Key words: calcified metastasis, cerebellar, ovarian cancer, surgery

Introduction

Intracranial calcified masses are usually associated with slowly progressive benign tumors (e.g., oligodendroglioma and meningioma), infectious diseases (e.g., tuberculosis, fungal infection, cysticercosis), and metabolic disorders (e.g., hyperparathyroidism).

Calcified metastases to the brain have been described in patients with squamous cell carcinoma of the lung,[7] adenocarcinoma of the lung,[3] sarcoma of the mediastinum,[13] squamous cell carcinoma of the cervix,[4] adenocarcinoma of the pancreas,[1] and non-Hodgkin's lymphoma.[16] Only four cases of calcified metastases to the brain arising from a primary ovarian carcinoma have been described.[2,6,11]

Generally, calcified brain tumors in those cases remained stable and did not progress. In fact, these patients had relatively benign clinical courses and prolonged survival. All four cases were multiple lesions and the interval between diagnosis of ovarian cancer and brain metastases was 3–12 months.

The present report describes a case of a patient with a single large cerebellar calcified metastatic tumor mimicking meningioma that arose from a primary ovarian cancer. This patient also had a relatively benign clinical courses and favorable survival, and the latent period was 10 years, which was longer than that in previous reported cases.

Case Report

A 33-year-old woman had a notable history of ovarian cancer diagnosed 10 years prior that was treated by surgical resection and adjuvant systemic chemotherapy. During a screening examination, a calcified cystic lesion was incidentally noted in the right cerebellar hemisphere on computed tomography (CT) (Fig. 1A). The patient declined any treatment for the presumed cerebellar tumor

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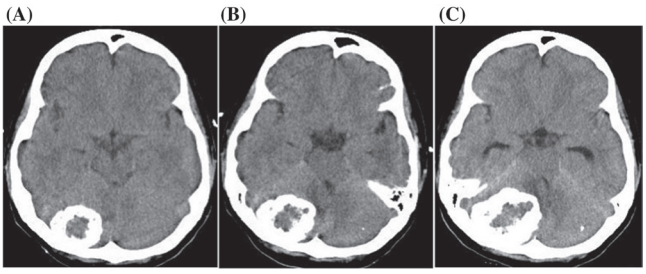

Fig. 1 Preoperative computed tomography (CT) scan showing calcified tumor in the right cerebellar hemisphere. A: A calcified tumor in the right cerebellar hemisphere was incidentally discovered 2 years before surgery. B: Follow-up CT 1 year later revealed slow growth of the tumor. C: The tumor grew progressively, compressing the brainstem. The ambient and quadrigeminal cisterns were not visualized, and the inferior horn of the lateral ventricle was enlarged.

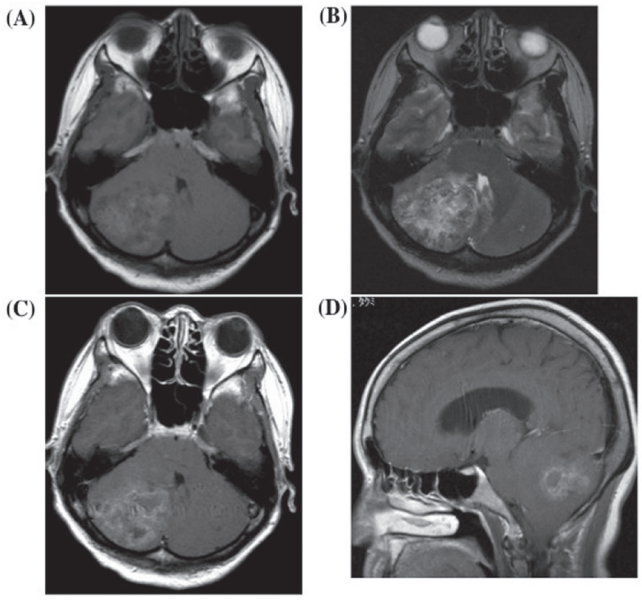

Fig. 2 Preoperative magnetic resonance imaging (MRI) showing a lesion in the right cerebellar hemisphere that was isointense on T_1-weighted imaging (A) and that was hyperintense on T_2-weighted imaging (B). The tumor was heterogeneously enhanced with gadolinium on axial (C) and sagittal images (D). Note the tonsillar herniation causing, compression of the brainstem and obstructive hydrocephalus.

and instead elected for serial follow-up. The size of the tumor gradually increased, while she was asymptomatic (Fig. 1B). Two years after the initial CT, she presented with headache and positional vertigo, and CT showed enlargement of the calcified tumor and hydrocephalus (Fig. 1C). Magnetic resonance imaging (MRI) showed a lesion that was isointense on T_1-weighted images and heterogeneously hyperintense on the T_2-weighted image with slight heterogeneous enhancement with gadolinium (Fig. 2A–C). Tonsillar herniation with obstructive hydrocephalus was also recognized (Fig. 2D).

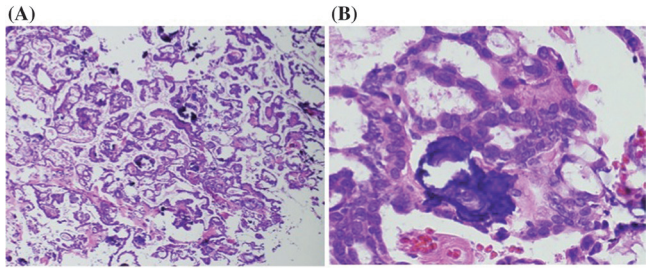

Fig. 3 Photomicrograph revealing mucinous tumor cells with acinar formation and papillary proliferation. Tumor contained psammomatous bodies in the stroma with atypical and mitotic cells (hematoxylin and eosin: A, ×40; B, ×200).

Informed consent was obtained, and right lateral suboccipital craniotomy was performed. The tumor was located subpially and appeared as a well-demarcated elastic hard mass that could be easily distinguished from the surrounding parenchyma. The tumor was gross totally removed. Histological findings revealed that the tumor cells were arranged in an acinar formation with psammomatous calcification in the stroma with atypical and mitotic tumor cells. The lesion was compatible with a diagnosis of serous mucinous adenocarcinoma (Fig. 3). MIB-1 index was 3% (data not shown) (MIB-1: Mindbomb E3 ubiquitin protein ligase 1). Postoperatively, the patient experienced improvement in her symptoms of headache and vertigo, and her postoperative course was uneventful. Postoperative CT and MRI revealed that the tumor was gross totally removed and demonstrated marked improvement in the tonsillar herniation and obstructive hydrocephalus (Figs. 4, 5). She got discharged two days after surgery. Subsequently, she received whole brain irradiation.

Discussion

Calcification of metastatic brain tumors is very rare and tends to occur in the basal ganglia and cerebellum, which are rich in endogenous iron and calcium.[9] At least two different mechanisms have been postulated to explain marked calcification of metastatic brain tumors.[6,10,12] First, reduced metabolism of degenerative or necrotic tissue can interrupt CO_2 production, making the lesions more alkaline than the surrounding tissues, thereby promoting calcification. Alternatively, calcification might be mediated by an increase in local alkaline phosphatase levels in degenerative tissues. In the presence of hypoxia, the equilibrium of extracellular calcium fails, resulting in an influx of calcium into the cell and subsequent calcium phosphate deposition. In a stable microenvironment, calcium phosphate may eventually be converted into

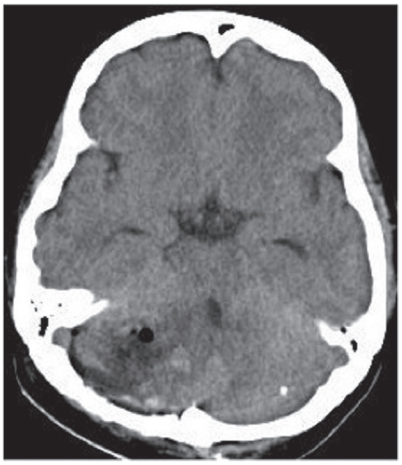

Fig. 4 Postoperative computed tomography (CT) scan showing that the calcified tumor was totally removed.

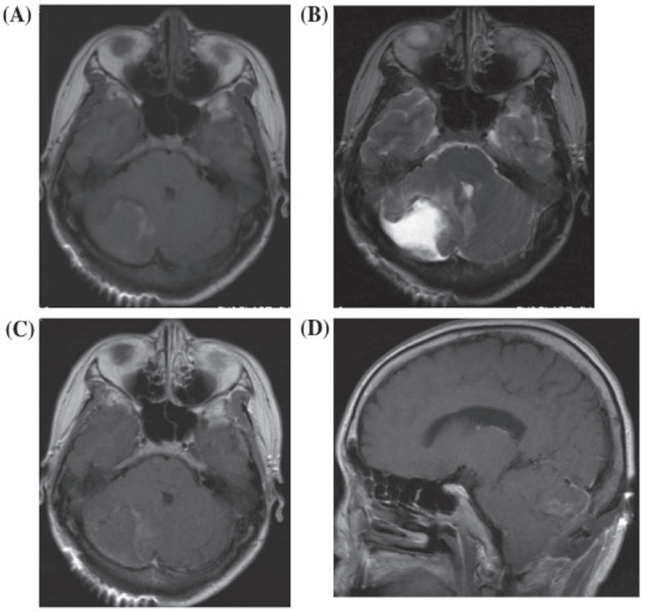

Fig. 5 Postoperative T_1-weighted (A) and T_2-weighted (B) magnetic resonance (MR) imaging, and MR image with gadolinium in the axial (C) and sagittal (D) planes, showing that the tumor was completely removed. Note that the brainstem was decompressed and that hydrocephalus had improved.

calcium hydroxyapatite, and crystal proliferation can follow, with the extension of calcification into the extracellular space. Calcification, therefore, may follow cell death and may be promoted by the presence of alkaline phosphate.

Generally, the differential diagnosis between metastatic brain tumors and benign intracranial tumors, including meningioma and oligodendroglioma, is exceedingly important, especially for treatment planning.[14] Calcified brain tumors are occasionally misdiagnosed in the absence of edema and contrast enhancement, resulting in a delay in diagnosis and/or treatment.[5,8,11]

In the present case, a patient with stage IIIc ovarian cancer treated with surgery and chemotherapy developed cerebellar metastasis 10 years after the initial diagnosis of her cancer. The cerebellar tumor was incidentally discovered by CT and, at the patient's preference, was followed conservatively. Initially, the tumor was considered to be a benign tumor, possibly a meningioma. However, slow growth of the tumor ultimately resulted in headache and vertigo due to tonsillar herniation and obstructive hydrocephalus at 2 years after detection of the brain lesion. On this basis, emergent surgical management was elected.

A previous study[17] using serial brain CT scans reported that size of the calcified metastatic brain tumors tended to increase at a rate slower than ordinary brain metastasis and can thereby be misinterpreted as meningioma.

Calcified brain tumors tend to remain quiescent without progression.[7,10] Considering the long periods of time required to develop calcium deposits, calcification appears more frequently in benign cysts or slow-growing tumors. On the other hand, loss of calcification indicates accelerated growth of malignant tumors.[5] Calcified metastatic brain tumors are very rare, but are also clinically important, as a delay in diagnosis and treatment can adversely impact survival.

Cancers arising in the lungs, colon, and breast are the most frequently reported primary cancer types that result in calcified intracranial metastases, while brain metastasis from ovarian cancer is comparatively rare. In the review of metastatic brain tumors arising from a primary ovarian cancer in the Department of Obstetrics and Gynecology at our institution, this phenomenon was noted in only 10 cases (0.24%) of 4,158 patients with ovarian cancer seen at our center over a period of 8 years (Table 1). In addition, only four cases of calcified brain metastasis arising from ovarian cancer have been reported thus far[2,6,11] (Table 2). The interval between treatment of the primary ovarian cancer and onset of the metastatic brain lesion in these cases ranged from several months to 10 years.[15] In our institution, the mean interval between diagnosis of the primary ovarian cancer and diagnosis of metastatic brain tumors was 1,271 days (3.5 years) (Table 1). As shown in Table 1, 6 (75%) of 8 cases of metastatic brain tumors arising from ovarian cancer in our institution had a single intracranial lesion. In contrast, all cases of calcified metastatic brain tumors arising from ovarian cancer in the literature had multiple lesions (Table 2), which favored the use of whole brain radiation therapy as the preferred therapeutic modality in those cases. Thus, the present case of a patient with a single calcified metastatic cerebellar tumor arising from ovarian cancer is extremely rare.

Due to simple statistics, increase in survival in response

Table 1 Summary of metastatic brain tumors arising from primary ovarian cancers in patients seen at our institution

Age	Stage for ovarian cancer	Location	No. of brain metastasis	Treatment for brain metastasis	Chemotherapy	Interval between diagnosis of ovary cancer and brain metastasis	Overall survival after treatment of brain metastasis	RPA	GPA
66	IV	Temporal	1	Subtotal removal & WBRT	taxol/CBDCA	24.5 months	23.9 months	I	3
33	IV	Brain stem	6	None	taxol/CBDCA	10.1 months	10 days	III	1
69	IV	Frontal	1	GKS	taxol/CBDCA	79.1 months	alive	I	3
57	IIIc	Occipital	1	Total removal & GKS	taxol/CBDCA	25.7 months	36.4 months	I	3.5
53	IIIc	Temporal	8	GKS	taxol/CBDCA	26.6 months	2.6 months	III	1.5
29	IIIc	Frontal	1	Subtotal removal & GKS	taxol/CBDCA	41.5 months	alive	I	4
60	IIIc	Cerebellar	1	Total removal & GKS	taxol/CBDCA	38.1 months	15.5 months	I	3
33	*IIIc*	*Cerebellar*	*1*	*Total removal & WBRT*	*GEM*	*114.5 months*	*alive*	*II*	*3*

Italics indicate the present case. CBDCA: carboplatin, GEM: gemcitabine, GKS: gamma knife surgery, GPA: graded prognosis assessment, RPA: recursive partitioning analysis, WBRT: whole brain radiation therapy.

Table 2 List of calcified metastatic brain tumors arising from primary ovarian cancer

Author (year)	Age	Stage for ovarian cancer	Location	Single/ multiple lesions	Chemotherapy	Interval between diagnosis of ovary cancer and brain metastasis	Treatment for brian metastasis
Burt TB et al. (1988)[2]	65	III	Cerebellar	Multiple	n.d.	3 months	n.d.
Burt TB et al. (1988)[2]	59	IIIc	Cerebellar, medulla	Multiple	n.d.	n.d.	Biopsy
Henriquez et al. (1999)[6]	69	IIIc	Frontal, parietal	Multiple	CBDCA/CPA	1 year	WBRT
Ricke J et al. (1996)[11]	52	IV	Frontal	Multiple	n.d.	5 months	Biopsy
Present case	*33*	*IIIc*	*Cerebellar*	*Single*	*GEM*	*10 years*	*Total removal & WBRT*

Italics indicate the present case. CBDCA: carboplatin, CPA: cyclophosphamide, GEM: gemcitabine , n.d.: not described, WBRT: whole brain radiation therapy.

to advances in chemotherapy may actually result in an increase in the incidence at which subsequent brain metastases (due to cancer relapse) are diagnosed. Interestingly in the present case, the interval between the initial diagnosis of the brain lesion and treatment of the cerebellar tumor was 2 years, which suggests a relatively indolent tumor phenotype that is similar to that seen for meningioma. Therefore, calcification might be an indicator of a relatively long survival in the case of metastatic tumor, provided the primary cancer is controlled.

In conclusion, complete tumor resection may be an acceptable approach for patients with calcified metastatic tumors both for therapeutic considerations and to obtain tissue for confirmation of histopathological diagnosis. Metastatic brain tumors can be calcified, and not only ovarian cancer but also other cancers should be considered within the differential diagnosis of calcified intracranial lesions to avoid any delay in diagnosis or treatment.

Conflicts of Interest Disclosure

The authors have no conflicts of interest.

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