Multiple Extracranial Metastases from Secondary Glioblastoma: A Case Report and Review of the Literature

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ABSTRACT
Glioblastoma represents extreme anaplasia in astrocytic tumors. In spite of this aggressiveness, extracranial metastasis of glioblastoma is very rare and has been documented in only a few patients in the literature. In this article, a 30-year-old woman with secondary glioblastoma associated with extracranial distant metastasis was presented. In September 2008, an intracranial lesion in the left frontal region was diagnosed by magnetic resonance imaging (MRI) after admission to the hospital by headache and seizure and subsequently resected. The histology of the lesion revealed an anaplastic astrocytoma (grade III). Upon recurrence of the tumor 7 months later, the patient underwent a second craniotomy for recurrence tumor resection. The histological diagnosis was glioblastoma. After radiotherapy and chemotherapy, cranial computerized tomography (CT) and whole body scintigraphy revealed metastatic lesions in the right cervical lymph nodes and the left ischium. A neck dissection and parathyroidectomy on the right side was performed. The cytomorphic and histological features of the tumor supported the diagnosis of metastatic glioblastoma.

KEYWORDS: Glioblastoma, Extracranial metastasis, Secondary glioblastoma, Prognosis

INTRODUCTION
Glioblastoma, the most common and most aggressive primary brain tumor, constitutes 50-60% and 12-15% of primary brain tumors and intracranial tumors, respectively (5). Glioblastoma may constitute either primarily or secondary to progression of low grade or anaplastic astrocytoma. These subgroups have different genetic characteristics, prognoses and treatment responses and they affect different age groups. Secondary glioblastoma patients are younger and they progress at a lower rate and they have better prognoses.

Extracranial metastasis is seen in only 0.44% of all neuroepithelial tumors and two third of these metastasis is formed by glioblastoma. Especially they spread to lymph nodes (51.4%), lungs and pleura (59.7%), bone (30.5%) and rarely to liver (22.2%). Other more rare extracranial metastatic places are spinal cord, skin, small bowel, parotid gland and other organ systems (6, 12).

Both extracranial metastasis and diagnosis of glioblastoma during pregnancy are rare entities. Here, a secondary glioblastoma pregnant patient with cervical lymph node and parotid gland metastasis is reported and discussed under the light of the literature.

CASE REPORT
A thirty-year-old female at the 22nd gestational week of her pregnancy was admitted to the neurosurgery outpatient department with the complaint of seizure and
frontal headache presented for a month. Her neurological examination was normal. Cranial MRI showed a 5x4 cm left frontal mass lesion (Figure 1A). The lesion was excised macroscopically totally in September 2008 (Figure 1B). The lesion was yellow-purple and elastic, and had hemorrhagic and necrotic areas in its center. Histopathological examination of the tissue revealed diffuse infiltration of atypical cells with ovoid, big and hyperchromatic nuclei and some of them with wide clear cytoplasm. There were mitosis, necrosis, diffuse S-100 and focal GFAP expression in the tumor cells. The histopathological diagnosis was concordant with anaplastic oligodendroglioma grade III.

Seven months later, the patient was admitted to the hospital with the complaint of right hemiparesis. Her cranial CT showed 4x4 cm mass lesion in the prior operation site with heterogeneous contrast enhancement and peripheral edema (Figure 1C, D). She was again operated on. Soft tissue particles that were gray-yellow-brown macroscopically contained microscopically atypical tumor cells with big, hyperchromatic, prominent nucleoli around the necrotic area. They were staining strongly with GFAP and p53. The final diagnosis after the pathological examination was glioblastoma. Following the surgical approach, radiotherapy (RT) and 7 cycles of Temozolomide treatment were performed.

Ten months later, a 7x5 cm mass lesion was detected in the right parotid gland. Her facial CT and whole body scintigraphy showed lymph nodes in the right cervical, preauricular, and retroauricular regions, and metastasis in the left ischium, respectively (Figure 2A, B). Plastic surgery department performed right paroidectomy and right radical neck dissection. The tumor cells were round shaped with hyperchromatic nuclei, clear cytoplasm showing prominent nucleoli in places and prominent pleomorphism. Tumor cells were stained with vimentin and S-100 focally and diffusely, respectively. Histological examination of the tumor cells in the parotid gland and the dissected neck region revealed glioblastoma diagnosis (Figure 3). She died 6 months after the paroidectomy and radical neck dissection operation.

**DISCUSSION**

Glioblastomas, on the molecular basis, have two subtypes as primary and secondary. Secondary glioblastomas form 5% of all the glioblastomas. Secondary glioblastomas are seen in younger patients than primary glioblastomas (9, 10). Our patient was a 30-year-old woman.

Secondary glioblastomas form as a result of astrocytoma and anaplastic astrocytoma gaining more malignant anaplasia. The mean time needed for a low-grade astrocytoma to
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The mean duration of survival in the secondary glioblastoma patients is 8.5 months and this is longer than the one in the primary glioblastoma patients (4.7 months) (5, 7). Fonkem et al. pointed that patients with metastasis to the lymph nodes and bone had the shortest time interval between diagnosis of the intracranial glioblastoma and detection of metastasis (2). In a recent natural history study the median overall survival time was detected as 10.5 months and the duration of survival in this patient after the first operation was 18 months (7).

Extracranial metastasis of glioblastomas is extremely rare. The lymph nodes and bone are common metastatic places while the parotid gland is a rare place for metastasis (8). There was metastasis both in the lymph node, bone, and the parotid gland. The lymph node metastasis has been reported especially in the cervical region on the same side with the previous craniotomy side (4). The patient's metastasis to the parotid gland and the cervical lymph node was contralateral to the previous craniotomy side.

The routes of extracranial metastasis in the glioblastomas are not clear. The hypoxic and proliferative zone of the glioblastoma has an angiogenesis-related breakdown of the blood-brain barrier and glioblastoma cells have direct communication with the systemic circulation (2). The metastases are seen commonly following surgery. This lead to the assumption that the tumoral cells gain may access to the lymphatics or veins during surgery. Another route is peritoneal metastasis via shunts (4). However, extracranial metastasis has been documented in patients who have not undergone any surgical procedure so metastasis via cerebrospinal fluid or blood is still possible (1, 3, 11). The presence of metastasis in the right cervical lymph node and bone makes lymphatic and hematogeneous routes most likely responsible for the metastasis.

The treatment of the glioblastomas includes generally surgery and adjuvant radiotherapy and chemotherapy. The survival may be lengthened significantly especially with
chemotherapy in the soft tissue metastasis and with the combination of three treatment modalities in the young patients. Even though several treatment approaches have been in clinical use, glioblastoma is still an aggressive tumor with unfavorable prognosis.

Despite of several theories to explain the mechanisms of distant metastasis of glioblastoma the issue has not been clarified yet. The diagnosis of extracranial glioblastoma metastasis has increased because of the modern diagnostic tools and prolonged survival of the patients.

REFERENCES