Neck Metastasis of Glioblastoma: Rare Case

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Abstract
Glioblastoma (GBM) is the most malignant primary intracranial tumor in adults. Metastases outside the central nervous system (CNS) are very rare. There are several factors for extracranial metastases, e.g., age during the diagnostic, lifespan, surgical treatment, and chemoradiotherapy. We present case, a female patient with glioblastoma single lesion neck metastasis in her left neck with excision tumor, radiotherapy, and chemotherapy and survive four years.

Introduction
Glioblastoma is the most malignant primary intracranial tumor in adults. The prevalence is 33-45% from all of primary malignancy intracranial tumor whose male is more prone than a woman.1,2,3 Global incidence of glioblastoma is rare, only comprising 3.2 per 100,000 population.1,2

Metastases outside CNS were uncommon in GBM, but it could occur with a frequency of 0.2% and can spread in the neck sites. The pathophysiology of extracranial metastases had poorly understood. The hypothesis from extracranial metastases of glioblastoma is a direct lymphatic connection, by the venous system and direct invasion by the adjacent structure like dura and bone.1

The outcome treatment is usually an unsatisfactory result. The therapeutic recommendation methods include a radical surgical procedure and combined with radio-chemo-therapy. The mortality with a median survival time only three months in untreated patients.3,4 Statistically, the combined therapy has significantly improved the total survival time from 12.1 to 14.6 months, and the 2-year survival rate was 26.5%, compared to 10.4% for radiotherapy alone.4 Racial influences revealed in
further prognostic according to recent research. According to the guideline, secondary glioblastoma is more frequent in older than 45 years and woman gender.

We present Glioblastoma with neck metastasis as a rare case.

Case report

A 37-year-old woman was referred to hospital with chief complaints of chronic progressive right hemiparesis since one year before admission, and accompanied by left asymmetrical face and dysarthria; in its clinical development also occur motoric aphasia, a protruding right eye, and blindness in both eyes, and a mass in the left neck.

The patient complains of frequent headaches for seven years before admission. Two years later, the patient emerged seizure, general tonic-clonic type, and the patient got a seizure therapy.

One year later, she presented with blurred vision in both eyes, chronic progressive cephalgia, right half body weakness, right half body numbness, and slurred speech. Computed Tomography (CT) Scan contrast demonstrated as a brain tumor (Fig.1). Craniotomy was performed in the left temporoparietal region for a brain tumor in another hospital and had a histopathological examination which revealed Glioblastoma WHO grade IV C71.2, M-94403/3. Post craniotomy Contrast CT scan still showed a present lesion with enhancement in the left temporal lobe cortex and reduced lesion size. Post-surgery evaluation has found extracranial herniation along 26 mm, through a 103 mm extensive defect in the left frontotemporoparietal os (Fig.2). After the surgery, the patient made an uneventful recovery and showed improvement symptoms which no headache and seizure. Imaging evaluation with MRI (Magnetic Resonance Imaging) was performed one month after surgery and revealed increasing of tumor size in the left frontotemporal lobe 35 x 58 x 38 cm and extracranial herniation was increased to 46 mm. Neuro-oncology criteria with RANO criteria showed a progressive disease type (Fig.3).

One year later, she presented with communication problems, speech disconnected, aggravate headaches and seizures increasing frequently. The patient also complains pain in the left neck, and there is a palpable mass lesion in the left neck that appears new single small mass 2x2 cm, tender, firm, and suspected lymphadenopathy. History taking revealed she did not routinely control to neurology outpatient clinic one year ago because the patient did not show symptoms. The head
CT scan contrast revealed GBM progression (Fig.4). We planned the surgical resection of the brain tumor, but the patient's family refuse, and she had received brain radiotherapy (20 Gy).

One year later, due to poor compliance of the patient and symptoms got worsening, the brain tumor resection approved by patient’s family and mass lesion in the left neck enlarge to 10 x 8 cm than previous with hyperemia, hard and irregular edges (Fig 5). Surgical resection performed and the histopathological finding showed an accordant recurrence of the GBM (WHO grade IV), suggesting IHK with GFAP, CK (Fig.6). Head CT scan evaluation after surgery showed a pneumocephalus in the left regio frontotemporal and solid lesion in the left regio occipital until the left colli suspect lymphadenopathy (Fig.7). Combined therapy chosen in concomitant chemoradiotherapy with a dose of radiotherapy 60 Gy in 30 fractions followed by chemotherapy temozolomide is given at 75mg/m2 PO daily for 42 days. Evaluation after concomitant radiochemotherapy with brain and neck MRI revealed cystic encephalomalacia in the left frontotemporal lobe with a solid lesion in it suggested a residual mass. The mass in the left posterior colli region suggested malignancy (Fig.8). Fine needle aspiration biopsy on left neck mass showed small round cell tumors indicated to a blastoma, suggest ICC LCA (Fig.9). Immunohistochemistry examination revealed positive glial fibrillary acidic protein (GFAP), and positive neuron-specific enolase (NSE) indicated metastatic GBM (Fig. 10). All pathological specimens, from the brain tumor and the neck mass, were confirmed as GBM.

The round discussion between neurologist, neurosurgeon, oncology surgeon, internist division of hematology/oncology, radiologist, pathologist assistant, decided combined therapy with 5 x 3gy colli radiotherapy and continued oral adjuvant temozolomide 150 mg/m2 on days 1-5 every 28 days planned for six cycles. The excision of tumor mass in the left neck planned. She remained in a stable condition during adjuvant chemotherapy with temozolomide. She showed improvement with a decrease of colli tumor size (Fig.11) and did not complain of headache, no seizures, good appetite, and an increase in weight of 3.5 kg. The patient did not control again. Three months later, the patient was aggravated and died because of the progression of the GBM.

Discussion
Epidemiology has shown the most prevalent primary glioblastomas as the majority of cases (>90%) and affects mostly in elderly with a mean age of 62 years old, yet even lower percentage still could appear in the case. Secondary glioblastomas are manifest in younger patients with a mean age of 45 years. In contrast, males were more frequent in women and had rapid progression from low-grade diffuse astrocytoma (WHO grade II) or anaplastic astrocytoma (WHO grade III). Diagnosis criteria of secondary glioblastoma needed clinical (neuroimaging) or histopathological (biopsy) evidence of progressively malignant astrocytoma.

The hypotheses about the GBM rarely metastases, it might be explained by the following reason: It is well known and broadly accepted that physical barrier around cerebral (dura mater, thickened basement membrane, and BBB/ blood-brain barrier) is a substantial barrier that will prevent tumor cells from spreading beyond the brain. There is no connection in perivascular spaces, and extracerebral fluid space made metastasis is burdensome.

However, 20% of GBM patients shown CTC (circulating tumor cells) in peripheral blood even without metastases. It seems that CTC hindered finding access to adjacent organs, may be explained by intrinsic properties of glial filament, the peripheral immune response of the host organ to neuroglial tumor cells may prevent metastasis extraneural, or lack of ECM (extracellular matrix proteins) such as collagen and fibronectin, which overexpressed in the hyperplastic blood vessels. Through hyaluronic acid and other glycosaminoglycans, which are the main components of the extracellular spaces, the tumor cells can migrate into the tissue. This property of the extracellular substrates can make hematogenous metastasis is rare. The other hypotheses are the absence of lymphatic vessels intracranial, and the connections between extracranial lymphatic vessels and the subarachnoid space are very sparse.

There are several factors for GBM neck metastases, e.g., first age during diagnosis, which is more prevalent for metastases at a younger age. In 1928 Davis was first to present a case with metastasis GBM. Recently from a published article found approximately 200 incidences of metastases in GBM patients. From epidemiology, it has found that younger and healthier patients are more prone to developing extracranial metastasis than elderly GBM. The second factor is lifespan, which better diagnostic and treatment had increasing survival years rate. The third factor is surgical treatment; almost 96% of patients with GBM metastasis have a
surgical treatment. Huang et al. described that extraneural spread after the neurosurgical operation. The tumor cells may access the blood circulation through the damaged blood-brain barrier (BBB), and tumor cell crossing the dura mater. Craniotomy with tumor resection is associated with the opening of the brain vessels and can be associated with the spread of tumor cells. In the present case, the patient underwent twice operations, which might increase the chance of distant metastasis, the direct invasion through the dura and bone or tumor cell migration along with the ventriculoperitoneal shunts. The fourth factors, the lymphatic cerebrospinal fluid drainage into the extraneural tissue (despite the absence of an identifiable lymphatic system in the CNS); The fifth factors, the venous invasion, either via the leptomeningeal sinuses or via the dural vein; The last factor is chemoradiotherapy, which causes excessive apoptosis and DNA injury to the brain tissue even in tumor cells cause inhibition of glioma angiogenesis. However, tumor cell invasion and proliferation increased to the brain tissue.  

As we knew, Guideline for GBM therapy consists of performing a craniotomy then followed by radiation and chemotherapy. Surgery’s primary goal is to remove as much of the tumor as possible without injuring the surrounding normal brain tissue needed for normal neurological function. After the wound healed, radiotherapy is beginning to selectively eradicate the remaining tumor cells that have infiltrated the surrounding normal brain tissue. The use of radiotherapy has improved outcomes and longer survival rates than surgery alone. Chemotherapy, as combined therapy with radiotherapy, is designed to eradicate tumor cells. Temozolomide is the current standard treatment for GBM. In our case, surgery and biopsy performed with a good result, but the second step therapy with radiotherapy not achieved because the patient did not routinely control and refused further medication. Recent research revealed that surgical therapy alone either with biopsy or brain resection has a survival rate 0.2 and 0.6 in 3 months respectively.

In the second event, one year later, it has shown to recurrent and progressive GBM. The medication was only with radiotherapy because the patient refused to brain resection. Recurrent glioblastoma is a possibility, especially in poorly compliance; the incidence of recurrent GBM inevitable after a median survival time of 32-36 weeks. In our case, recurrent is more than 36 weeks; it must be due to progressive symptoms that occur and previous therapy. Best medical option to recurrent GBM was combined therapy surgical and chemoradiotherapy; recent research has shown re-
resection followed by adjuvant treatment and systemic treatment had significantly longer survival than patients receiving supportive care (7.3 and 11.0 versus 3.1 months respectively [HR 0.46 (p<0.001) and 0.36 (p<0.001)].

In the third event, recurrent GBM was getting worst, and combined therapy was applied. Even though in optimal medicamentosa, after round discussion between expert new approach was taken and got a good result.

The survival rate in GBM patients was devastating. Tamimi et al. have shown only a few patients survive 2.5 years and less than 5% of patient survive five years following therapy. The median duration of patient survival estimated between 12 and 18 months with maximal therapy, but those without any intervention die soon after diagnosis. In a large retrospective study, Scott et al. revealed that 2.2% of the cohort survived for >2 years, but the overall five-year survival rate is only <10% with a mortality rate of almost 100%. In our case, it showed 4 years of survival rate and achieved good progression, although the patient was poor compliance.

This case is to be considered an acceptable case of GBM extracranial metastases, Weiss established that which included: (1) the presence of single histologically characteristic a primary brain tumor must be proven; (2) the clinical histories were due to this tumor; (3) a complete autopsy must be performed to exclude the possibility of any other primary tumor; and (4) the presumed extracranial metastases.

In this case, the GBM patient with neck metastatic, and the patient got surgery two times, radiotherapy concomitant with chemotherapy. The patient survived for 2.5 years, which is longer than most GBM patient survival years rate.

Conclusion

The patient neck metastatic glioblastoma presented the possibility the leading risk factor was recurrent surgeries, a long lifespan, and chemoradiotherapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, patients gave their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will
not be published and outstanding efforts made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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