

Extra neural metastasis of glioblastoma multiforme: A literature review

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Abstract

Extra-neural metastases of glioblastoma multiforme are uncommon with unidentified metastatic mechanism. There is no consensus over optimum treatment regimen. The current narrative review was planned to illuminate the presence criteria, sites of metastatic spread, incidence, mechanism, risk factors and management.

Keywords: Glioblastoma multiforme, Extra-neural metastases, Spread, Mechanism, Risk factors.

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Introduction

Glioblastoma multiforme (GBM) is a very common and malevolent brain tumour due to fast development and undesirable prognosis.¹⁻³ Generally, glial origin of the GBM was initially identified by Virchow in 1863. GBM is an erstwhile term which was coined in 1914.^{4,5} Among adults, the malignant glioma is held responsible for about 60% of all primary brain tumours (PBTs) and can be segregated into 3 kinds on histological basis: GBM, anaplastic astrocytoma, and anaplastic oligodendroglioma (OG).⁶

The GBM remains an incurable disease, with an average overall survival (OS) rate of 20 months regardless of treatment modality.⁷⁻⁹ After diagnosis, the survival rate among patients is only 5.5%. The GBM includes primary as well as secondary subtypes which develop through several hereditary pathways that affect the patients at various ages along with differences in the outcomes.¹⁰⁻¹³

The primary GBMs are responsible for 80% GBMs and take place among the elderly, with an average age of 62 years, and the secondary GBMs take place from OG or lower-grade astrocytoma among young patients with an average age of 45 years. Normally, the secondary GBMs are found inside the frontal lobe, have less amount of necrosis and

enhanced prognosis than the primary GBMs.^{10,11}

The recent global standard regarding nomenclature and diagnosis of the gliomas is the classification of World Health Organisation (WHO). It categorises the gliomas in grades 1-4 based upon histopathological standards. The GBM is considered most intrusive, aggressive and undistinguishable tumour form, and is labelled Grade-4 by WHO.¹⁴⁻¹⁶

Extra-neural metastases

The extra-neural metastasis (ENM) of PBTs is uncommon. In 1926, it was elucidated that gliomas almost do not metastasise outside the central nervous system (CNS).¹⁷

Presence criteria

Their existence is described by the Weiss criteria as follows:^{6,18,19}

1. Metastatic lesion meets the histological attributes of CNS tumour.
2. Clinical course must propose that initial indications were because of CNS tumour.
3. Total necropsy must be performed to rule out any additional primary tumour.
4. Primary tumour morphologic characteristics and metastatic lesion should be similar.

Presently, the criteria 1, 3 and 4 are generally accepted for ENM diagnosis.^{18,19}

Sites of metastatic spread

Metastatic spread of GBM, although rare, most commonly involve pleura, followed by liver, bone and lymph nodes (LNs).^{4,20} Bone marrow, skin and heart have been reported as possible sites of spread as well.²¹⁻²⁵ Patients with lung metastasis have the worst prognosis.²⁶

Incidence

The incidence of ENM due to primary intracranial gliomas is expected to be <2% and it usually occurs in the later stages of the disease, and mostly takes place following craniotomy for tumour excision.^{6,22-29}

Mechanisms

The pathogenesis of extra-neural spread is not well known. However, several theories have been postulated regarding

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their rare incidence; absence of lymphatics in the CNS, dense connective tissue encircling dural veins, thin-walled intracerebral veins and absence of communicating channels between extra-cerebral fluid area and perivascular area, blood-brain barrier (BBB) action, and extremely reduced survival.^{24-26,30,31}

The high incidence of ENM after neurosurgery reported was likely secondary to inadequate closure of dura that may result in direct communication between tumour cells and extra-meningeal vessels and lymphatics.^{6,32} Pasquier et al. hypothesised that negative pressure in vessels opened intra-operatively may cause aspiration of cancer cells into the blood stream.³³

Local factors of host organ

Local factors, such as tumour cell composition, cytokines, growth factors, adhesion molecules, extra-cellular matrix constituency, cell motility, cytoskeleton and enzyme action, play a major role in tumour metastasis.^{26,34,35} The most prominent role is played by extra-cellular matrix proteins fibronectin and laminin, those produced by cerebral tumours, like laminin, hyaluronic acid, tenascin and vitronectin, and other cytokines.^{26,36-38} Vascular basement membrane (VBM) protein is considered a defensive factor against tumour invasion.³⁹

Also, the tumour cells discharge enzymes that are engaged in tumour attack through degrading VBM. These enzymes are the tissue proteinases, like Urokinase-type Plasminogen Activator (uPA), cathepsin B and membrane metalloendoprotease.²¹ The malevolent glioma cells are not able to exude such kind of enzymes that of able to cause degradation of VBM.^{21,37}

Cerebrospinal route

Metastases to cerebrospinal fluid (CSF) are much frequent with OGs and medulloblastomas. As 500-550mL CSF is formed daily; the cells ingoing CSF may find dissemination express route.⁶ It has been suggested that less-distinguished tumour cells as well as less frequency of glial fibrillary acidic (GFA) protein appearance contribute to an elevated propensity to spread in CSF.⁴⁰

Haematogenous pathway

Metastasis is considered a multilevel procedure, involving cell disconnection from primitive tumour, adhesion and arrest in an area of target organ; exodus in blood vessels; micro-metastases formation; eructation in organ stroma followed by tumour development and neoangiogenesis causing formation of explicit tumour.^{21,24,25} Craniotomy contravenes CNS-inherent defensive system and could cause tumour cells to enter the blood vessels. It is the diverse route and major pathway for spleen, bone and lung

metastases. The vertebral ENM takes place when glioma cell metastases go into Batson plexus and spread in the CSF. Blood could be supplied by Batson plexus to inferior deep vein and to sacral and lumbar spines, enabling ENM formation to liver, lung as well as sacral and lumbar spines. Connections may take place between meningeal as well as craniocervical venous system, the last system being attached to internal intraspinal veins that flow back towards anterior and posterior cervical spines, and may cause ENM in the axis.⁴¹

Also, the BBB may play an important part in ENM occurrence through acting to oppose the migration of malevolent glioma cells. This is made from the non-fenestrated strongly packed endothelial cells intently attached to the astrocyte foot process. The electron research has demonstrated that BBB is interrupted at the tumour site.⁶

Lymphogenic route

It was postulated that the dearth of lymphatic vessels in CNS forms a tumour spread barrier. An important portion of CSF drains in the CNS lymphatic vessels. Clinical assessments, such as facial swelling or nasal congestion after CSF shunt obstruction, support the notion that the CNS lymphatic vessels exist in reality.⁴² However, there is no confirmation regarding the existence of CNS lymphatic vessels, and it may explain an elevated ENM prevalence in the cervical/retro-auricular LNs.^{21,24,25}

Continuous spread

Several temporal lobes GBMs may impulsively attack and obliterate the temporal bone, and thus cause ENM formation. Also, the cranial nerves and intracranial blood vessels could facilitate tumour cell extension in the extra-dural gaps.⁶

Genetic considerations

A molecular inherent analysis among 6 cases of the ENM of GBM assessed both metastatic and primary lesions, and the deoxyribonucleic acid (DNA) was examined regarding genetic modifications mostly observed in GBM (EGFR-{ Epidermal Growth Factor Receptor} intensification, allelic loss of 1p, 10q, 19q, CDKN2A { Cyclin-Dependent Kinase Inhibitor 2A }/p16 erasures, and TP53 { Tumor Protein 53} alterations). Among 4 cases of TP53 alterations, uncommonly, 2 dissimilar TP53 modifications were seen in the metastatic and primary lesions or in metastatic cancers. It would recommend that the metastatic lesions signify sub-clones' emergence that were undominant in brain glioblastoma. Incidence of ENM from the GBM may be encouraged through TP53 modifications as well as different clonal selection.⁴³

Risk factors

The ENM risk factors of GBM were unclear.⁴⁴ However, several neurooncologists have confirmed that younger age, extended survival period, frequent recurrence, sarcomatous constituent and high-level tumour cytology are associated with ENM.^{32,45} It is broadly acknowledged that neurosurgical procedures related to brain vessels' opening may damage BBB that makes haematogenic ENM of the brain tumour. A study indicated that almost all (96%) patients with ENMs of GBM had experienced neurosurgical interventions earlier.³²

In 1985, a study reported 282 ENM cases of CNS tumours. The study focussed on differences between adults and children and discovered that among children especially, medulloblastoma metastasised outside CNS. Among adults, in contrast, glioma was the more frequent brain tumour to spread extracranially. Among 79 patients of gliomas, 88% obtained craniotomy that, as per patients, played a significant role in metastases, together with CSF diversion.⁴⁶

A study reported that a boy with a left thalamic GBM aged 7 years developed abdominal spread that manifested as severe abdominal distention, seven months and two weeks following left and right occipital VPS (Ventiuloperitoneal Shunt) catheter placement for disruptive hydrocephalus. Computed tomography (CT) of abdomen demonstrated diffuse ascites along with carcinomatosis confirmation. Further workup showed broad leptomeningeal carcinomatosis engaging cauda equina and cord.⁴⁷

A study on GBM ENM with 5 gliosarcoma and 110 glioblastoma cases had 70.4% males and overall mean age 38.2 years. Time passed between diagnosis of spread and mortality was significantly enhanced among patients undergoing surgical treatment, while time from primary tumour identification to mortality was considerably enhanced among patients obtaining radiation treatment. Time passed from spread to mortality and identification to mortality was considerably more among patients getting chemotherapy. Liver was found to be the metastatic location related to overall least survival. The study stressed the significance of surgical resection level as well as utilisation of adjuvant radiation therapy and chemotherapy for long survival.⁴⁸

A case of primary GBM was reported by a study. The patient was male and aged 46 years. He developed scalp metastasis and subsequent several pulmonary metastases, 6 and 18 months following primary identification, respectively. Despite targetted therapy and salvage chemotherapy for scalp spread, the patient ultimately died due to respiratory failure because of several pulmonary

metastases 20 months after the preliminary identification. The study emphasised the need for meticulous follow-up comprising serial magnetic resonance imaging (MRI) of the brain and relevant investigations inferior to incidence of extracranial indications. Also, the prophylactic craniospinal treatment was suggested for patients with CSF seeding elevated risk, if ventricles were opened in surgical treatment, or if tumour was closely contacted with CSF.⁴⁹

A case series in 2021 regarding ENM glioblastoma had 10 patients of whom 9 were diagnosed with ENM glioblastoma and 1 with gliosarcoma. At identification, patients were aged 14-73 years, while 7 were male and 3 were female. The overall average survival from preliminary identification and from ENM identification was 19.6 and 5 months, respectively. Most common ENM location was bone, and the other locations were lymph nodes, lung, dura, soft tissues and liver. The study concluded that numerous risk factors occurred for ENM of gliosarcoma and glioblastoma, including sarcomatous dedifferentiation, interruption of the normal anatomic barricades during the surgical resection as well as mutations of the tumour suppressor gene.⁵⁰

A GBM case of temporal lobe along with subsequent bone and liver spread was reported in 2006. Metastases of bone and liver were treated successfully with temozolomide and then with docetaxel and carboplatin. After 2 years of first identification, local symptomatic recurrence took place. Hence, a fractionated stereotactic radiation therapy was carried out. Due to liver metastases relapse, the patient received chemotherapy along with etoposide, adriamycin and cyclophosphamide. The visceral spread was found stable, but the patient died due to progression three years after initial identification. It was found that liver spread of GBM could efficiently be treated through chemotherapy.⁵¹

In 2015 a study described a patient aged 20 years who presented with subacute-onset headache. An increasing right temporal lesion was discovered on MRI, signifying an elevated-level glioma as the initial identification. Operation was carried out attaining lesion GTR (Gross Total Resection). The patient was treated with chemotherapy and adjuvant radiotherapy. After 5 months of initial surgical treatment, the patient complained hacking cough and chest pain. The CT of thoracoabdominal and pelvis demonstrated two-sided lung penetrates with pleural manifestation, pancreatic nodule as well as numerous vertebral lytic lesions. The biopsy was carried out of the lung lesions. The pathological identification was metastatic GBM. The patient died after 8 months of initial identification.⁵²

A study in 2021 reported that 6 cases were diagnosed with original investigations of glioblastoma, glioblastoma with

primitive neuroectodermal tumour-like constituents, atypical meningioma, anaplastic ependymoma, haemangiopericytoma and myxopapillary ependymoma. At initial diagnosis, patients' mean age was 44 years. Time interval between the first identification and metastatic disease appearance was 3 months to 19 years. All the FNA (Fine Needle Aspiration) analyses were accurately rendered. Immunohistochemistry (IHC) was utilised among four cases to support identification. All patients had previous surgical treatment at the site of primary tumour. The ENM site among 4 patients was ipsilateral parotid/buccal area. In the midline site, 2 primary tumours developed ENM within the scapular area.⁵³

Management

No standard of care is available at recurrence; although, radiotherapy, surgical treatment and systematic treatment together with chemotherapy/bevacizumab are all possible alternatives, depending upon the condition of a patient. Palliative as well as supportive care remain significant consideration during the course of the disease with a multimodality approach for management. There is a need for optimum therapeutic alternatives, and there have been significant advancements exploring the immunotherapy and appropriate oncology techniques. Biological factors, like BBB, unique tumour and protected microenvironment, represent great challenges for the development of new therapies. Inventive clinical trial designs with biological marker enrichment strategies are required to eventually enhance the outcome of patients with glioblastoma.⁵⁴

Conclusion

The ENMs are very rare and lethal sequelae of primary CNS malignancies. However, the exact ENM mechanism is not well recognised. GBM can spread to extra-neural organs. Rapid diagnoses, aggressive management as well as careful utilisation of CSF diversion techniques are needed to enhance both the duration and quality of life of the patients.

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