ORIGINAL SCIENTIFIC ARTICLES

Recurrent Epithelioid Glioblastoma in a Young Patient With Systemic Lupus Erythematosus: a Case Report

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INTRODUCTION

Glioblastoma multiforme (GBM) represents the most malignant form of brain tumor and is relatively common, comprising nearly almost 20% of all primary malignancies of the central nervous system1. GBM is a WHO grade IV tumor with several variants, depending primarily on their genetic signature and on the predominant histological architecture. Among the variants of GBM, epithelioid glioblastoma (E-GBM) has been one of the more recently described. This tumor, documented to be highly malignant and clinically aggressive, has been separated from close variants and thus differentials, pleomorphic anaplastic xanthoastrocytoma, rhabdoid GBM, small cell and giant cell GBM, GBM with neuroectodermal differentiation, and gliosarcoma2.

Autoimmune diseases have been linked with increased risk of CNS complications, from the constant effects of chronic inflammatory milieu. Systemic lupus erythematosus (SLE) has been associated with several CNS abnormalities, hence the terms CNS lupus or neuropsychiatric lupus. Likewise, SLE has been repeatedly associated with CNS malignancies in several cases and case reports.

To date, there is paucity in the reported cases of malignant brain tumors, especially rare variants, in patients with SLE. While it is hypothesized that the inflammatory milieu that bathes the brain in a dynamic microenvironment that influences the incidence of rare variants of GBM. clinicians should be mindful, as treatment is challenging: it may either induce exacerbation of autoimmunity or cause undertreatment of the malignancy. This complex interplay births curiosity into the enigma of autoimmunity and oncology.

In this particular report, we highlight the case of a patient with SLE who developed E-GBM. We identify the clinicopathologic features of the tumor present in the patient and explore the known aspects of the crosstalk between SLE and E-GBM.

CASE REPORT

A 20-year-old Filipino female, with systemic lupus erythematosus since 2017 and compliantly maintained on hydroxychloroquine, presents with intermittent but progressive headache in the right frontal region, gradually worsening over the past year, temporarily and partially relieved by intake of over-the-counter pain medications. One month prior to current consult, the patient developed new-onset left-sided body weakness and numbness, and new-onset nocturnal seizures witnessed by relatives as tonic-clonic jerky movement of both extremities with associated drooling of saliva, with associated post-ictal disorientation and urinary incontinence. Consult was done with her rheumatologist, who advised neurology referral. Cranial MRI showed an aggregate of complex right frontal lobe masses, with predominantly cystic and heterogeneously enhancing solid components, associated with peri-lesional edema and subfalcine and transtentorial herniation (Figure 1). She was referred to Neurosurgery

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and underwent craniectomy with gross total tumor excision.

Histopathology of the tumor revealed a plethora of findings including marked cellular atypia with enlarged, hyperchromatic to vesicular, highly pleomorphic nuclei with prominent nucleoli, irregular nuclear contour, and eosinophilic neoplasm disposed in solid sheets and nests (Figure 2).

Immunohistochemical staining likewise showed variability of results: staining focally positive for GFAP, Synaptophysin, CAM5.2, EMA, SMA, OLIG2, but was negative for SALL4, STAT6, and IDH1. Neuropathology concurred the case as epithelioid glioblastoma.

Post-operatively, repeat imaging showed resolution of tumoral mass effects. Seizures were controlled, and with rehabilitation, the patient's deficits gradually improved. However, the patient was eventually lost to follow-up. At the interim, the patient's headache, focal weakness and numbness, and seizures recurred in rapid progression. Repeat imaging showed tumor recurrence. Treatment options offered to the family include tumor debulking, radiation therapy, and chemotherapy. However, the patient's family opted for palliative care. Three (3) months post-operatively, with best supportive management, the patient expired.

DISCUSSION

Officially recognized by the World Health Organization as a variant of GBM in 2016, E-GBM is a rare but highly aggressive subtype of glioblastoma, earning a WHO grade IV classification1. In literature, E-GBM represents a variant with increased morphologic and genetic heterogeneity.

Of the uncommon types of glioblastoma, E-GBM is the rarest and occurs mostly in the second to the third decade of life, with a female predominance (2:1), and has been associated with very dismal prognosis despite aggressive treatment and management2. Local data on its accurate prevalence and incidence remains lacking.

Two case series, Wang, et al. (2020)3 and Sun, et al. (2021)4, show that in most cases, headache was the most common presenting manifestation, followed by dizziness, nausea and vomiting, seizures, and focal weakness or numbness. The tumor demonstrates anatomic predilection to the cerebral hemispheres, particularly to the frontal and temporal lobes. Few risk factors were identified, and smoking was associated with poorer prognosis.

The tumorigenesis of E-GBM is poorly understood, but has been postulated as a result of malignant transformation of anaplastic pleomorphic xanthoastrocytoma5, another rare variant of GBM, characterized by an array of mitotically-active and histomorphologically diverse cells. E-GBM has been classically associated with BRAF V600E mutations, although many other alterations including TERT mutation, IDH1 mutation, and MGMT promoter methylation were described. A genomic study done by Mondia, et al. (2023)6 revealed instability of the genetic make-up of E-GBM, and the microenvironment associated with this type of tumor, highlighting how distinct cells predominate in either the glioma section (myeloid cell line) and the epithelioid section (CD4+ lymphocytes, NK cells). The pathoetiologic mechanisms underlying these genetic idiosyncrasies of E-GBM are poorly understood and warrant further investigation.

Grossly, E-GBM comprises of mixed solid to cystic mass that may be multifocal and multicentric, almost mimicking a metastatic process. Histologically, E-GBM shows highly heterogenous cells encompassing large epithelial cells with abundant cytoplasm, spindle cells, multinucleated giant cells, eccentric and pleomorphic nuclei, and increased mitotic activity. Immunohistochemical staining show variable positivity to cytokeratin, GFAP, IDH, desmin, BRAF, p53, ATRX, INI, s100, and Ki-67, with IDH-1, INI-1, and BRAF being most consistently observed4. Radiographically, E-GBM is difficult to distinguish from other malignant brain

Figure 1. Cranial MRI images (T1, T2, FLAIR, and T1 with Contrast, at the level of the insula, *top*, and at the level of the centrum semiovale, *bottom*) showing three complex masses in the right frontal lobe, with cystic and heterogeneously enhancing components.

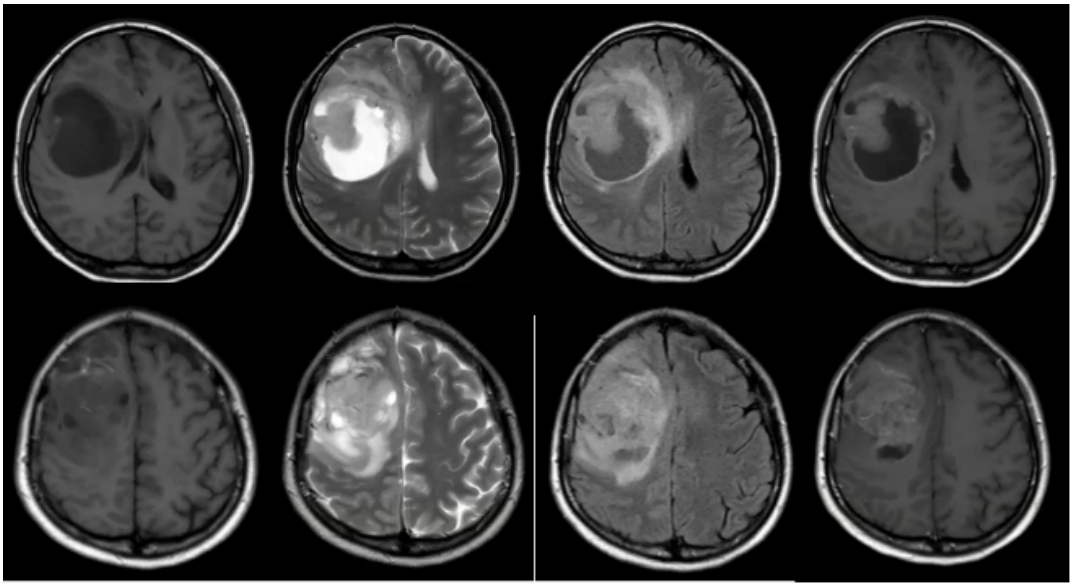
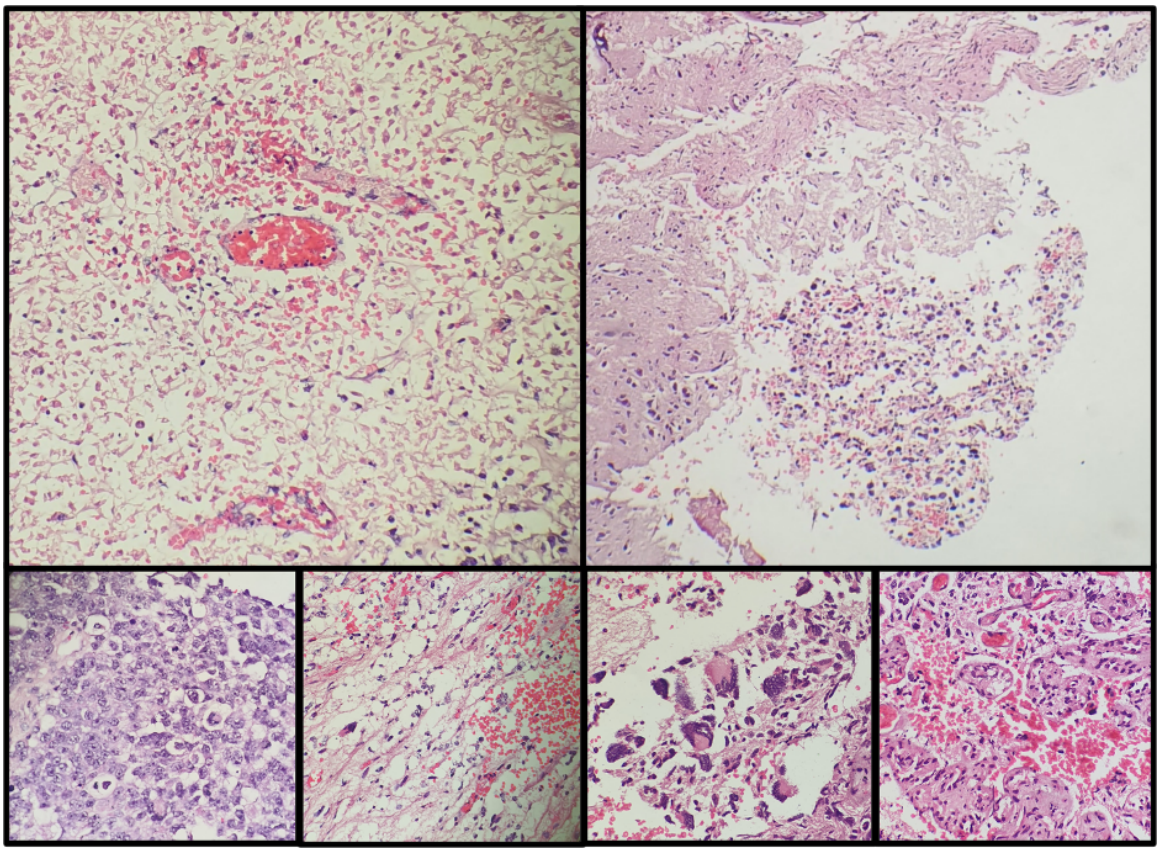


Figure 2. Sections of the tumor show absence of endothelial proliferation (*upper left*) yet with brain invasion (*upper right*). The tumor shows a wide array of cellular morphologies from large epithelioid cells with abundant cytoplasm and vesicular nuclei, spindle cells, multinucleated giant cells, and highly mitotically active cells in nests (*bottom row, left to right*).



tumors. It is seen on MRI as a well-delineated, ring-enhancing lesion associated with cystic degeneration ("small nodule in a large cyst"), nodular enhancement, meningeal invasion, and possible cerebrospinal fluid dissemination7. Hemorrhagic and calcific foci may also be seen. The variability of the tumor's histological, immunohistochemical, and radiographic signature makes it difficult to absolutely commit to diagnosis.

Maximal surgical excision of the tumor remains the mainstay of treatment, but adjunctive radiotherapy and chemotherapy with temozolomide have shown utility in improving survival rates3,4. Molecular therapy using BRAF kinase inhibitors, specifically dabrafenib, has been used and showed clinically significant curative effect, but may require more evidence to conclusively indicate improved outcomes.

The prognosis of E-GBM is very poor, with a mean survival rate of less than a year from diagnosis3,4. Leptomeningeal spread through CSF may warrant investigation of the spine for metastases. Tumoral bleeding, although rare in other forms of GBM, may be common. Metastases may involve the skin, salivary glands, lung, live, thorax, bone, and the abdomen. MGMT promotion methylation status, presence of BRAF V600E mutation, and TERT mutation have been identified as possible molecular prognosticators, all of which, when present, signal poorer prognosis.

The association between this specific type of GBM and SLE has not been well established. Autoimmune diseases have been generally associated with increased risk, and SLE in particular has been cited to be an inciting factor in the initiation and progression of GBM, although the mechanisms underlying their relationship remain unclear8. In other primary brain tumors that have been documented to be in consonance with SLE, it is postulated that malignancy arises from the chronic inflammatory state, oncogene overactivation, and dysfunctional immunoregulatory milieu that the brain is constantly subjected to that are attributable mechanisms9,10. Treatment should be well-considered, as this may induce exacerbation In E-GBM, this remains a theory.

CONCLUSION

To our knowledge, this is the first case of E-GBM that has been documented in a young adult female with SLE at our institution. Diagnosis and treatment remain challenging, given its intratumoral variability in imaging, pathologic, and molecular features. Owing to its aggressive, invasive, metastatic, and recurrent potential, the tumor carries a dismal prognosis. To date, novel targets to treatment require further inquiry.

CONSENT

A written consent was obtained from the patient's relatives for publication of the case report and the accompanying images. A copy of the written consent is available for review.

REFERENCES

1. Li J, Ling X, Lai M, Hu Q, Shan C, Cai L. [Clinicopathological features for epithelioid glioblastoma: A newly defined tumor by the 2016 World Health Organization Classification of Tumors of the Central Nervous System]. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2018 Apr 28;43(4):398-402. Chinese. doi: 10.11817/j.issn.1672-7347.2018.04.010. PMID: 29774876.
2. Mallick S, Benson R, Venkatesulu B, Melgandi W, Rath GK. Systematic Review and Individual Patient Data Analysis of Uncommon Variants of Glioblastoma: An Analysis of 196 Cases. Neurol India. 2022 Sep-Oct;70(5): 2086-2092. doi: 10.4103/0028-3886.359222. PMID: 36352613.
3. Wang S, He Q, Zhang Q, Guan B, Zhou X. Clinicopathologic features and prognosis of epithelioid glioblastoma. Int J Clin Exp Pathol. 2020 Jul 1;13(7): 1529-1539. PMID: 32782671; PMCID: PMC7414508.
4. Sun K, Zhou X, Li T, Zuo M, Li J, Liu Y. Clinicopathological characteristics and

treatment outcomes of epithelioid glioblastoma. Neurosurg Rev. 2021 Dec;44(6):3335-3348. doi: 10.1007/s10143-021-01492-7. Epub 2021 Feb 17. PMID: 33598819.

5. Lin Z, Yang R, Zheng H, Li Z, Yi G, Wu Q, Yang C, Huang G. Pleomorphic xanthoastrocytoma, anaplastic pleomorphic xanthoastrocytoma, and epithelioid glioblastoma: Case series with clinical characteristics, molecular features and progression relationship. Clin Neurol Neurosurg. 2022 Oct; 221:107379. doi: 10.1016/j.clineuro.2022.107379. Epub 2022 Jul 21. PMID: 35932588.
6. Mondia MWL, Kritselis MA, Donahue JE, Elinzano H, Sarangi S, Bryant D, Capelletti M, Korn WM, Yu E, Yan S, Toms SA, Wong ET. Dimorphic glioblastoma with glial and epithelioid phenotypes: Clonal evolution and immune selection. Front Neurol. 2023 Jan 10;13:1017087. doi: 10.3389/fneur.2022.1017087. PMID: 36703629; PMCID: PMC9871816.
7. Zhao JP, Cui CX, Wang JC, Su HW, Duan CF, Liu XJ. Multimodal MR Features of 8 Cases of Epithelioid Glioblastoma. Biomed Res Int. 2020 Oct 16;2020:9586806. doi: 10.1155/2020/9586806. PMID: 33123592; PMCID: PMC7586153.
8. Zhang YH, Li Z, Zeng T, Pan X, Chen L, Liu D, Li H, Huang T, Cai YD. Distinguishing Glioblastoma Subtypes by Methylation Signatures. Front Genet. 2020 Nov 24;11:604336. doi: 10.3389/fgene.2020.604336. PMID: 33329750; PMCID: PMC7732602.
9. Su L, Ding M, Chen L, Li C, Lao M. Primary central nervous system lymphoma in a patient with systemic lupus erythematosus mimicking high-grade glioma: A case report and review of literature. Medicine (Baltimore). 2018 Jun;97(23):e11072. doi: 10.1097/MD.0000000000011072. PMID: 29879076; PMCID: PMC5999485.
10. Clarke AE, Pooley N, Marjenberg Z, Langham J, Nicholson L, Langham S, Embleton N, Wang X, Desta B, Barut V, Hammond ER. Risk of malignancy in patients with systemic lupus erythematosus: Systematic review and meta-analysis. Semin Arthritis Rheum. 2021 Dec;51(6):1230-1241. doi: 10.1016/j.semarthrit.2021.09.009. Epub 2021 Sep 30. PMID: 34710720.