

## Glioblastoma Occurring as Second Primary in a Treated Case of Diffuse Large B-Cell Lymphoma

### Abstract

Glioblastoma as second primary malignancy (SPM) has been reported after prostate cancer, meningiomas, Hodgkin's lymphoma. We report an extremely rare case of glioblastoma as SPM, occurring after remission of diffuse large B-cell lymphoma (DLBCL). Fifty-year-old male presented with loss of consciousness followed by right-sided weakness. He was treated with chemotherapy for DLBCL of the cervical lymph nodes, 5 years back. Present scans revealed well-defined intra-axial lesion in the left parietal lobe, suggestive of central nervous system (CNS) involvement by lymphoma. Left parieto-occipital craniotomy was performed and microscopic examination revealed the tumor to be Glioblastoma, WHO Grade IV. The tumor cells were positive for glial fibrillary acid protein and negative for leucocyte common antigen. He was treated by radiotherapy and temozolomide. Pathologic examination is a must for CNS lesions. Had it not been for the biopsy, the patient would have been treated as a recurrence of CNS lymphoma by chemotherapy and would have probably succumbed.

**Keywords:** Chemotherapy, diffuse large B-cell lymphoma, glioblastoma, non-Hodgkin's lymphoma

### Introduction

Glioblastomas are aggressive brain tumors of glial origin with ionizing radiation as the only possible etiologic factor known till date.<sup>[1]</sup> These usually occur as primary neoplasms with dismal prognosis. These have rarely been reported to occur as second primary malignancy (SPM) following prostate cancer, meningiomas, medulloblastomas, Hodgkin's lymphoma, acute lymphoblastic leukemia, pituitary adenoma, and craniopharyngioma.<sup>[2-5]</sup> Among the SPM reported in patients of non-Hodgkin's lymphoma (NHL), the incidence of brain tumors is extremely low, ranging from 1% to 3%.<sup>[6-10]</sup>

The treatment of NHL has revolutionized over the last two decades with chemoradiotherapy, allowing greater number of survivors. On long-term follow-up, some of these patients have developed SPM.

We hereby report an extremely rare case of glioblastoma as a SPM, occurring 5 years after complete remission of diffuse large B-cell lymphoma (DLBCL), who had not received radiotherapy for the same.

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### Case Report

A 50-year-old man, slaughter house worker by occupation, presented in August 2019 with an episode of loss of consciousness with subsequent right-sided weakness and giddiness. He was a tobacco chewer since the past 20 years. He was not a known diabetic or hypertensive and was presently not on any medications. The past history revealed that he was a treated case of DLBCL 5 years back. He had then presented with enlarged lymph nodes in the left supraclavicular region and multiple abdominal lymph nodes. His disease was confirmed on biopsy and his bone marrow was uninvolved. For the same, he was treated with six cycles of Dose Adjusted Rituximab, Etoposide, Prednisolone, Vincristine, Cyclophosphamide, Doxorubicin (R-EPOCH) regimen. In view of low cell counts during chemotherapy and an episode of pneumonitis, he was administered granulocyte colony stimulating factor and pegfilgrastim. Positron emission tomography scan after four cycles did not show the presence of any metabolically active disease in the body and was suggestive of complete remission. He completed six cycles of chemotherapy in July 2014 and was not

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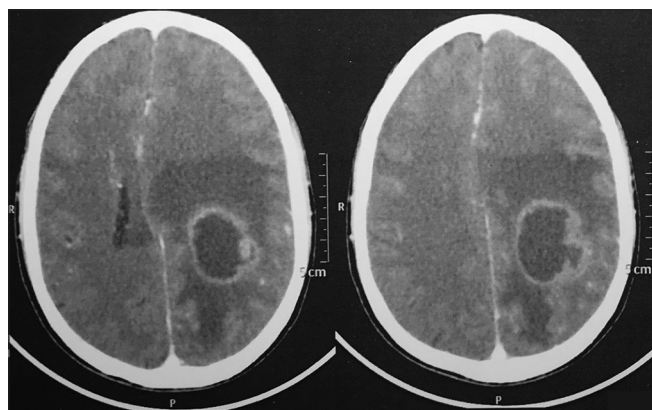
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given any radiation. He was on regular follow-up since then, without any evidence of recurrence.

On examination for his present complaints, he had reduced power in the right upper limb along with increase in tone. Clinically, a relapse of lymphoma with involvement of the central nervous system (CNS) was suspected. Magnetic resonance imaging showed a 5.5 cm × 4.8 cm × 3.2 cm well-defined hypodense lesion in the left parietal lobe with rim enhancement on postcontrast study. Disproportionate perilesional edema was seen extending into splenium and causing mass effect in the form of effacement of lateral ventricle, subfalcine herniation, and midline shift of 8 mm towards the opposite side [Figure 1]. These features were suggestive of CNS involvement by lymphoma. Bone marrow biopsy and examination of the cerebrospinal fluid did not show involvement by lymphoma cells.

A stereotactic biopsy was planned and left parieto-occipital craniotomy was performed. Intraoperatively, the tumor was



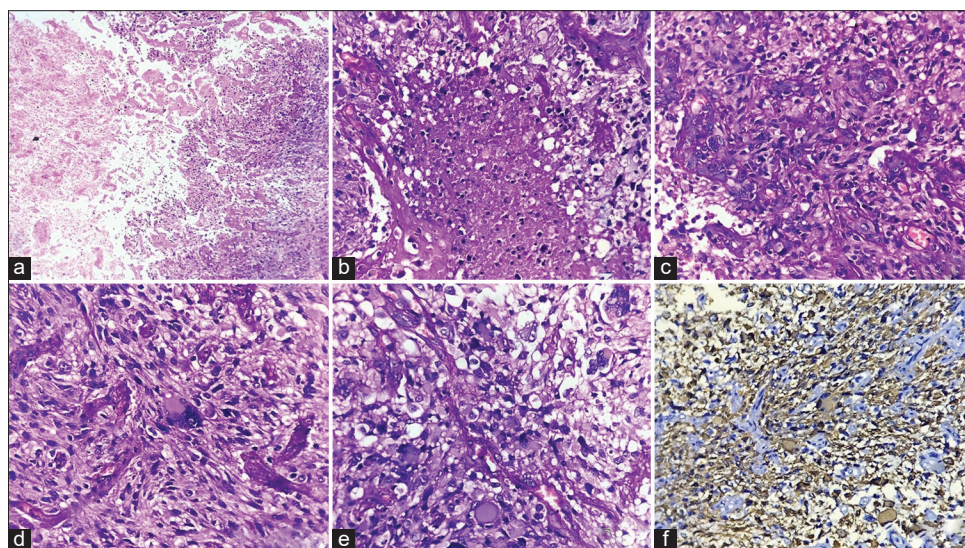
**Figure 1:** T1-weighted magnetic resonance imaging image showing a well-defined hypodense lesion in the left parietal lobe with rim enhancement, disproportionate perilesional edema, and midline shift of 8 mm

soft suckable, moderately vascular with cystic fluid and showed perilesional edema.

For pathologic examination, multiple gray brown, soft to firm tissue bits were received, aggregating to 5 cm × 4 cm × 0.8 cm. The largest bit measured 2.5 cm × 1 cm × 0.8 cm and on cut surface showed gray white areas, along with few yellowish necrotic and focally congested areas. Microscopic examination revealed a highly cellular tumor with varied morphology. Tumor cells were arranged in sheets amidst a fibrillary background. Some of the tumor cells were polygonal with abundant eosinophilic cytoplasm and vesicular nucleus having irregular contours, while other cells were spindle shaped and arranged in fascicles with plump hyperchromatic nuclei. Multi-nucleate tumor giant cells and bizarre cells were also seen. There was marked nuclear pleomorphism and anisocytosis. Many atypical mitotic figures, areas of palisaded and nonpalisaded necrosis along with microvascular proliferation were seen [Figure 2a-e]. Adjacent cerebral cortex included in the biopsy showed evidence of tumor cell infiltration. No atypical lymphoid cells were seen. On immunohistochemistry (IHC), the tumor cells were positive for glial fibrillary acid protein (GFAP) [Figure 2f] and negative for Leucocyte Common Antigen (LCA). Hence, an impression of a high grade malignant glial neoplasm favoring Glioblastoma – WHO Grade IV was given. The patient received external beam radiotherapy to partial brain at a dose of 59.4 Gy, 33 fractions over 6.5 weeks and concurrent treatment with temozolomide. The patient remains free of disease, two months post-radiotherapy and has been advised regular follow-up.

## Discussion

A SPM is defined as the occurrence of a second malignant



**Figure 2:** (a) Markedly cellular tumor with areas of infarcted necrosis (HE, ×100). (b) Areas of palisading necrosis surrounded by microvascular proliferation (HE, ×400). (c) Microvascular proliferation (HE, ×400). (d and e) Cellular tumor with cells showing marked pleomorphism and mitosis. Multinucleate and bizarre cells seen against a fibrillary background (HE, ×400). (f) Tumor is positive for glial fibrillary acid protein immunohistochemistry (×400)



neoplasm either simultaneously (synchronous) or after an interval (>6 months) of the diagnosis (metachronous) of a histologically distinct index tumor. For a tumor to be labeled as SPM, it should fulfill the three criteria as defined by Warren and Gates, namely malignant nature of each tumor be confirmed histologically, both tumors should be geographically distinct and metastasis of one from the other has to be ruled out.<sup>[11]</sup> Our case fulfilled all the three criteria where in both the tumors were biopsied, examined histologically and the same confirmed by relevant IHC. The sites for both being distinct, in that DLBCL involved the supraclavicular and abdominal lymph nodes and glioblastoma affecting the left parietal lobe of the brain. Metastasis or involvement of brain by lymphoma was ruled out on microscopic examination since the tumor showed cells with elongated hyperchromatic nuclei in a fibrillary background. Areas of classic palisading necrosis and microvascular proliferation were also seen. The same were confirmed by GFAP IHC, which was positive in the tumor cells. No cells with lymphoid morphology were identified and LCA was negative.

The reported prevalence of SPM varies among different geographic regions, ranging from 16% to 18%.<sup>[12,13]</sup> This can be due to effective treatments leading to longer survival of patients with cancer. The occurrence of second tumors can be attributed to either long-term side effects of chemotherapy or radiotherapy. Besides this, genetic predisposition, environmental factors, immune status, and lifestyle factors such as alcohol consumption or cigarette smoking play equally important role as etiologic factors.<sup>[13,14]</sup>

In the surveillance, epidemiology, and end results program, the incidence of SPM after NHL was reported to be 7%.<sup>[15]</sup> A study from Australia reported an increased risk of malignancies of tongue, lip, bladder, thyroid, melanomas of skin, and soft-tissue sarcomas in treated cases of NHL.<sup>[6]</sup> Okines *et al.* reported an incidence of 1.32% second cancers in treated cases of NHL, 6 months after their primary diagnosis. Bronchial, breast, colorectal, skin, and stomach carcinomas were most commonly observed in their cohort. Among the 33 patients with NHL, only a single male patient was reported to have a brain tumor.<sup>[7]</sup> In a meta-analysis comprising of 19 studies, 12 reported a positive association between risk for SPM post-NHL. They concluded that there is 1.88-fold increase in risk of SPM in NHL survivors as compared to the general population and attributed this risk to chemotherapeutic agents especially alkylating agents, alone or with radiotherapy.<sup>[10]</sup>

As per the thorough literature search, Glioblastoma after NHL has not been exclusively reported. However, CNS tumors have been reported as SPM in treated cases of NHL. According to one study, the standardized incidence ratios for solid tumors after NHL were 1.65 and were highest (40.8) for spinal meningiomas. As per their analysis, earlier age at treatment and therapy related damage could be contributing factors for SPM.<sup>[9]</sup> Morton *et al.* reported eight

cases of brain and CNS tumors among the 873 patients with SPM following DLBCL. Prostate followed by lung and bronchial carcinomas were the most common SPM amongst the DLBCL patients.<sup>[16]</sup>

DLBCL and Burkitt's lymphoma are considered to be the aggressive types of NHL. However, these have shown to respond well to chemotherapy regimens. Treatment with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone or R-EPOCH followed by radiotherapy, if required, is the current approach and is personalized for every patient depending on the stage at the time of diagnosis. With advent of the monoclonal antibody rituximab, the treatment for NHL has revolutionized with mortality rates reducing by almost 30% when compared to the prerituximab era.<sup>[17]</sup> One study compared the incidence of SPM in the pre- and post-rituximab era and concluded that the incidence of acute myeloid leukemia, melanomas, and thyroid cancers increased significantly in the postrituximab era. They also observed increased rates of subsequent Hodgkins's lymphoma, liver, and lung cancer in treated cases of DLBCL.<sup>[18]</sup>

The various chemotherapeutic drugs have different mechanisms of action and act at the molecular level to destroy the tumor cells. Their effects on normal cells are a concern. Etoposide and doxorubicin are DNA Topoisomerase II inhibitors and cause apoptosis of cancer cells.<sup>[19,20]</sup> Vincristine is a vinca alkaloid and acts by attaching to the tubulin protein, and thereby prevents cell division during metaphase. It has been shown to cause cranial neuropathy.<sup>[21]</sup> Cyclophosphamide belongs to the class of alkylating agents and acts through its metabolite phosphoramidate mustard. This metabolite forms interstrand and intrastrand DNA cross linkages and leads to cell apoptosis.<sup>[22]</sup> These drugs have been reported to have various long-term side effects. However, CNS penetration of these drugs is minimal considering their inability to cross the blood brain barrier.

Many authors have studied the mechanisms causing neurotoxicity and cognitive dysfunction by chemotherapeutic agents. Wardill *et al.* proposed three mechanisms for the same. Direct cytotoxicity, oxidative stress and peripherally derived cytokines disrupt the blood-brain barrier, thus can lead to the potential adverse events of chemotherapeutic agents by allowing their entry into the CNS and also cause neuroinflammation.<sup>[23]</sup> This disruption of the blood-brain barrier, allowing entry of chemotherapeutic agents that can cause carcinogenic events in the brain can be hypothesized to cause Glioblastoma post-DLBCL therapy in our case. However, more studies are required in this regard to prove such causal association. Alternatively, we understand the occurrence of glioblastoma in our patient could be just a SPM without any association with DLBCL or its therapy.

Glioblastoma is the most aggressive astrocytic glioma and accounts for about 15% of intracranial neoplasms.

**Table 1: Glioblastoma as second primary in the literature**

Authors (years)	Age (years)/sex	Primary tumor	Latency (years)
Symss <i>et al.</i> (2006) <sup>[25]</sup>	7/male	ALL	3
Joh <i>et al.</i> (2011) <sup>[5]</sup>	17/female	ALL	10
Grace <i>et al.</i> (2015) <sup>[2]</sup>	70/male	Prostate cancer	4
Pichon <i>et al.</i> (2017) <sup>[26]</sup>	45/male	Melanoma in situ on the skin and nodular sclerosing Hodgkin's lymphoma	10
Labuschagne and Chetty (2019) <sup>[3]</sup>	74/female	Meningioma	1.5
Present case (2020)	50/male	Diffuse large B-cell lymphoma	5

ALL – Acute lymphoblastic leukemia

It is most commonly seen in the elderly age group with male predominance. It is a fatal disease with median survival outcomes of 15–18 months after diagnosis.<sup>[24]</sup> Many etiologic factors have been studied but have failed to establish causal relationship, except for exposure to ionizing radiation.<sup>[1,4]</sup> In our patient, this tumor occurred at a relatively younger age.

Glioblastoma as a SPM has been rarely reported as shown in Table 1. Accordingly, a single case has been reported after Hodgkin's Lymphoma but even after thorough literature search, we could not find GBM to be reported after NHL – DLBCL. However, reverse scenario has been reported wherein DLBCL was reported in a patient with GBM, who was treated with temozolomide and radiotherapy.<sup>[27]</sup> Some authors have reported co-existence of multiple, primary brain tumors wherein GBM was seen in association with pituitary adenoma.<sup>[28]</sup> Since not much literature is available regarding the etiology of GBM as a SPM, its occurrence by chance cannot be entirely ruled out.

Although SPM have been reported in survivors of DLBCL, the occurrence of brain tumors in this setting is a rare event and more studies are required in this regard to determine its etiology.

#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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#### Conflicts of interest

There are no conflicts of interest.

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