

CASE REPORTS

Intracranial hemorrhage from metastatic CNS lymphoma: A case report and literature review

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Abstract

Metastatic brain lymphomas, which belong to secondary central nervous system lymphomas, usually originate from primary tumors of the bone marrow, testis, or orbit. Gastrointestinal lymphomas commonly metastasize to the lung or heart. We report here a case of brain hemorrhage due to metastasis from primary gastrointestinal diffuse large B-cell lymphoma (DLBCL). A 30-year-old male presented with headache. He was diagnosed to have gastrointestinal lymphoma 6 months earlier, and treated with gastrointestinal surgery. Pathological diagnosis was DLBCL. A PET-CT scan immediately after gastrointestinal surgery demonstrated no brain metastasis. On admission to the ward, imaging of the brain showed right temporoparietal hematoma. In the ward, the patient deteriorated with impaired consciousness. Repeat brain imaging showed enlargement of the hematoma. He underwent right temporoparietal craniotomy for the removal of a hematoma, and tumor nodules adherent to the cortex was found. Pathology confirmed a metastatic DLBCL in the brain. Literature review showed that this was the first reported case of brain hemorrhage from metastatic lymphoma. Metastatic central nervous system lymphoma should be considered as a differential diagnosis in patients with a history of gastrointestinal lymphoma presenting with neurological symptoms.

Keywords: Diffuse large B-cell lymphoma; gastrointestinal; brain metastasis; brain hemorrhage

INTRODUCTION

Lymphomas are hematological malignancies with extranodal manifestations in approximately 40% of cases.¹ Central nervous system (CNS) lymphoma includes primary CNS lymphoma and secondary CNS lymphoma.² Secondary CNS lymphoma is generally considered as CNS involvement in lymphoma that was not evident at the initiation of treatment for systemic lymphoma outside the CNS.³ Metastatic brain lymphoma is considered a secondary CNS lymphoma.^{2,3} The primary sites of metastatic CNS lymphoma include the nasal cavity or paranasal sinus⁴, peripheral blood^{4,5}, orbit,⁴ bone marrow^{4,6}, testis⁴, bone⁴, and breast.⁷ To the authors' knowledge, there are no previous reports of brain metastasis from gastrointestinal lymphoma. Primary gastrointestinal non-Hodgkin lymphoma (PGI NHL) is one of the most common types of extranodal lymphomas, accounting for 30-50%

of all extranodal lymphomas.⁸ Gastrointestinal lymphoma is known to metastasize to the lung or heart.^{9,10}

Intracranial hemorrhage is a neurological emergency usually caused by high blood pressure, vessel malformation, or arterial aneurysm. Intracranial hemorrhage may also be caused by tumors such as glioma.¹¹ There is no previous reports of cerebral hemorrhage due to metastatic lymphoma.

We report here a case of brain metastasis from primary gastrointestinal diffuse large B-cell lymphoma (DLBCL) with hemorrhage. The literature on hemorrhage in cerebral lymphoma was reviewed.

CASE REPORT

A 30-year-old male presented at our institution with complaints of headache for four days. His medical history revealed a diagnosis of

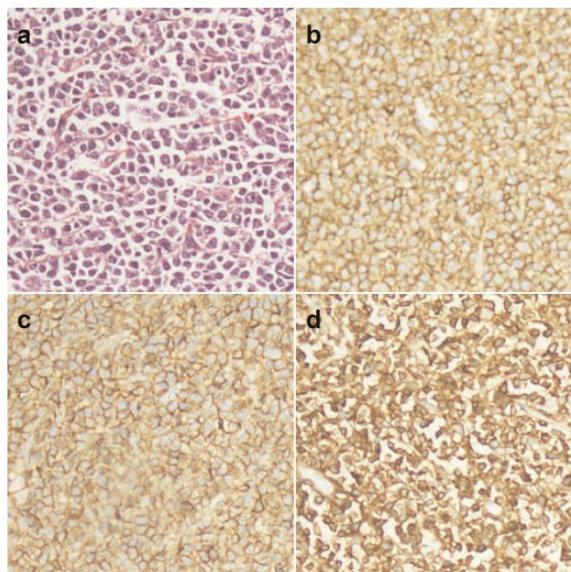


Figure 1. Immunohistochemistry-confirmed gastrointestinal diffuse large B-cell lymphoma (DLBCL): (a) hematoxylin and eosin staining (magnification, $\times 20$); the tumor was (b) LCA-positive (magnification, $\times 20$), (c) CD20-positive (magnification, $\times 20$), and (d) CD79a-positive (magnification, $\times 20$).

gastrointestinal lymphoma and gastrointestinal surgery six months earlier; pathological diagnosis was DLBCL (Figure 1). The initial stage of the lymphoma was stage III B. Whole body positron emission tomography–computed tomography (PET-CT) scan immediately after surgery did not demonstrate any brain metastasis. The initial risk score of CNS metastasis was intermediate risk (NCCU guidelines: NHL 2016.3). The patient underwent six courses of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) chemotherapy after abdominal surgery. The remission status of the initial 6 cycles of chemotherapy was CR (CT-Based Response).

The patient had no history of hypertension, brain trauma, congenital abnormality, and was not administered any immunosuppressive agents. Clinical examination and laboratory investigations were unremarkable, including a negative serologic test for human immunodeficiency virus (HIV).

Computed tomography (CT) of the brain demonstrated a right temporoparietal hematoma of mixed density with no mass effect, edema, or midline shift (Figure 2). Magnetic resonance imaging (MRI) of the brain revealed that the hematoma was hypointense on T1-weighted imaging and mildly hyperintense on fluid-attenuated inversion recovery sequence and T2-weighted imaging (Figure 3). The patient was diagnosed with hematoma in the cortex of the right temporoparietal lobe. Dynamic contrast

enhanced CT angiography (CTA) of the blood vessels in the brain showed no abnormality.

The hematoma was initially managed conservatively. However, on day six of hospitalization the patient's condition rapidly deteriorated and his Glasgow Coma Score was 8/15. CT scan showed the enlarged hematoma accompanied by edema in the right temporoparietal lobe (Figure 4). Right temporoparietal craniotomy was performed immediately, a 35-ml hematoma was removed. During surgery, it was noted that some gyri were covered with tumor nodes, the largest of which was 1.0 cm in diameter. Based on the patient's history of gastrointestinal lymphoma, the hematoma was thought to be caused by metastasis. Therefore, gross resection of the hematoma was performed, and some of the abnormal brain lesions were removed. After surgery the patient's neurologic status became normal.

Histopathologic examination of the tissues revealed that the cortex included a portion of abnormal, small round cells with prominent nuclei. Immunohistochemistry showed that cells were positive for B-cell markers (CD20 and CD79a) and negative for T-cell markers (CD3) (Figure 5). The pathologic diagnosis was NHL DLBCL with acute hemorrhage.

The patient was discharged after surgery and went to another hospital in another province. Because of poverty and side effect of chemotherapy, the patient's family refused further

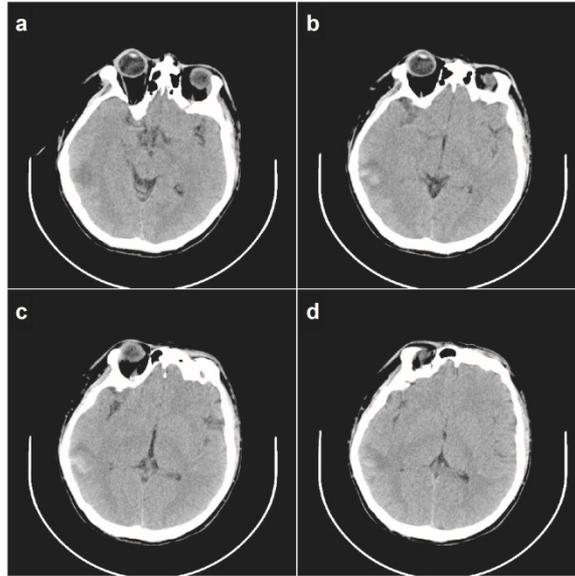


Figure 2. Multi-slice CT imaging showing hemorrhage in the right tempoparietal lobe

chemotherapy. At four months post-surgery, the patient had tumor dissemination and died. No autopsy was performed.

DISCUSSION

Gastrointestinal lymphoma is a malignant tumor.¹² Our patient was diagnosed with gastrointestinal DLBCL based on histopathology following gastrointestinal surgery. The postoperative PET-CT scan revealed no metastasis to the CNS. This was considered a definitive diagnosis, as PET-CT was thought to be able to exclude CNS metastasis.¹³ The patient presented to our hospital complaining of sudden headache. CT of the brain demonstrated a cerebral hematoma. The patient had no history of hypertension, and the cause of the hematoma was unknown.

The primary sites of metastatic CNS lymphoma are usually the bone marrow^{4,6}, testis⁴, or orbit.⁴ As there have been no reports of gastrointestinal lymphoma metastasizing to the brain, the hematoma due to metastatic lymphoma were not suspected. This case showed that CNS metastasis

in DLBCL is not solely depends on the site of the tumor. CNS involvement should be suspected when the patient with lymphoma presents with CNS symptoms. Right tempoparietal craniotomy was performed in our patient with removal of the hematoma and tumor nodules. Pathology confirmed DLBCL and hemorrhage in the brain.

The median survival time (MST) of secondary CNS lymphoma is less than 6 months.³ Our patient died four months after undergoing right tempoparietal craniotomy. Some evidence suggests that BCL-2 overexpression confers resistance to chemotherapy, and Ki-67 overexpression is associated with poor prognosis in patients treated with R-CHOP.¹⁴⁻¹⁶ The present case was Ki-67 (+) >90% and BCL-2(+) 80%.

Bleeding in secondary CNS lymphoma is rare. Therefore, we reviewed the literature on hemorrhage in cerebral lymphoma (Table 1). PubMed and Web of Science databases were independently searched from inception to February 1, 2017 by two reviewers using

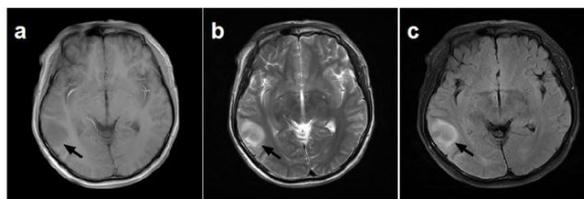


Figure 3. MRI showing a hematoma that was (a) hypointense on T1-weighted imaging, and (b) mildly hyperintense on T2-weighted imaging and (c) fluid-attenuated inversion recovery sequence.

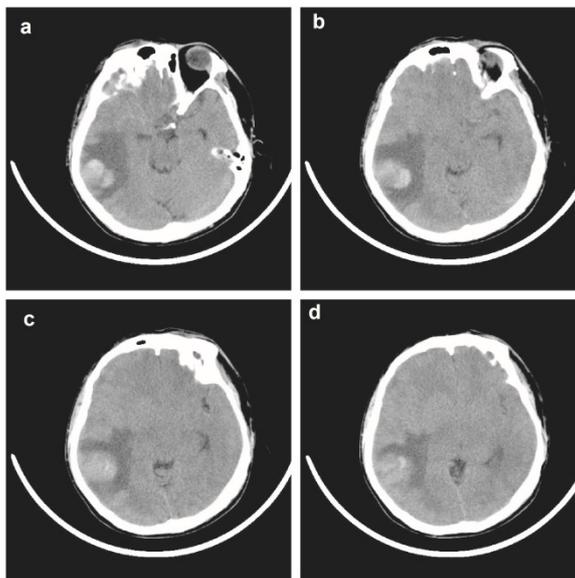


Figure 4. CT scan showed the enlarged hematoma accompanied by edema in the right temporoparietal lobe.

the following keywords and subject terms: “lymphoma”, “diffuse large B-cell lymphoma”, “non-Hodgkin lymphoma”, “brain”, “cerebral”, and “central nervous system” in combination with “hemorrhage”, “hematoma”. The search revealed nine reports with seven cases of intracranial hemorrhage in primary CNS lymphoma, one case each of relapse CNS lymphoma, and systemic lymphoma. The mean age of the patients was 60. 7 years (range: 29-96 years), suggesting

that bleeding in CNS lymphoma occurs more in the elderly patients. There were six males and three females. The lymphomas of seven patients originated from B cells. Five patients were vascular endothelial growth factor (VEGF) positive. VEGF is thought to induce spontaneous hemorrhage in CNS lymphoma.¹⁷ Only one patient was HIV positive. In six patients, the hemorrhage was located in the frontal lobe, and in one patient each, the hemorrhage was located

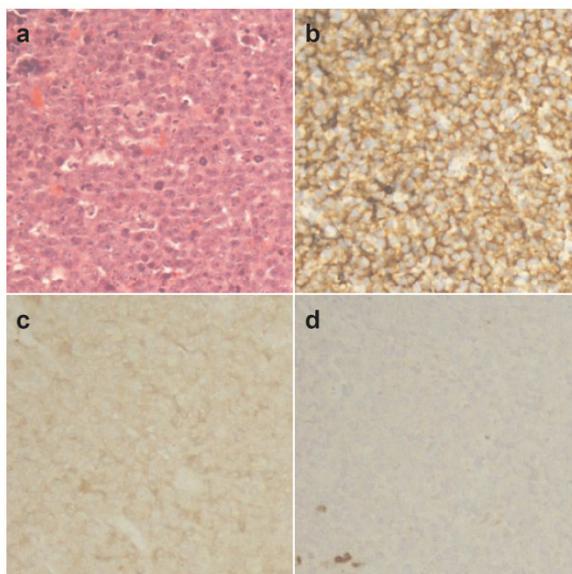


Figure 5. Immunohistochemistry confirmed that the abnormal cortex originated from DLBCL: (a) Hematoxylin and eosin staining (magnification, ×20); the tumor was (b) CD20-positive (magnification, ×20), (c) CD79a-positive (magnification, ×20), and (d) CD3-negative (magnification, ×20).

Table 1: Clinical features of previously reported patients of CNS lymphoma with hemorrhage

Case	Author	Age/ Gender	Clinical presentation	Physical examination	Hemorrhage location	CT/MRI	Diagnosis	Origin	Treatment after hemorrhage	Treatment before hemorrhage	VEGF test	HIV test	Result
1	Fukui <i>et al.</i> ²⁰	29/M	Oral dyskinesia, headache, nausea	Left-sided facial droop	Lt. Fr	T2-hypointense T1-mixed signal intensity	Primary CNS lymphoma	ND	Only biopsy	ND	Not examined	Positive	ND
2	Rubenstein <i>et al.</i> ¹⁷	55/M	Right arm tonic clonic seizures	Right upper extremity weakness	Lt. Posterior Fr	ND	Primary CNS lymphoma	diffuse large cell non- Hodgkin's lymphoma	Left posterior frontal craniotomy Chemotherapy and radiotherapy	ND	Intense reactivity	ND	Remission discharge
3	Kim <i>et al.</i> ²¹	49/F	Sudden deterioration of mental status	Stuporous mental state, right hemiparesis grade 0	Lt. Fr	Mass effect of left frontal lobe, midline shifting to the right	Primary CNS lymphoma	B-cell	Chemotherapy and radiotherapy	ND	High immuno- reactivity	Negative	Discharge
4	Kimura <i>et al.</i> ²²	57/F	Drowsy	Mild right hemifacial palsy, mild right hemiparesis, and hyperreflexia in the right extremities without pathologic reflex	Lt. Fr	T1-Hyperintense, T2-hypointense	Primary CNS lymphoma	B-cell	Left frontal craniotomy	intrathecal chemo- therapy	Positive	Negative	Discharge
5	Kim <i>et al.</i> ²³	75/M	Sensory aphasia	ND	Lt. temporoparietal	ND	Relapsed CNS lymphoma	B-cell	Chemotherapy and radiotherapy	ND	Positive	ND	ND
6	Low <i>et al.</i> ²⁴	62/M	Mild right upper limb, facial weakness	Right facial droop, grade 4+/5 power in the right upper limb	Lt. parietofrontal chronic subdural hematoma	T1-hypointense, T2 and FLIR- mildly hyperintense	Primary dural lymphoma	B-cell	left frontoparietal craniotomy	ND	Not examined	Negative	Continue oncology and radiology treatment
7	Matsuyama <i>et al.</i> ²⁵	67/M	Comatose	ND	Lt. Fr	Intracerebral bleeding in the left frontal lobe, midline shifting to the right side	Primary CNS lymphoma	B-cell	Emergency endoscopic removal of the hematoma	chemo- therapy	High levels of immuno- reactivity	Negative	Died
8	Yang <i>et al.</i> ²⁶	56/F	Lower extremities Weakness, progressive cognitive decline	Cognitive deficits, positive left babinski sign	Lt. T	T1-hypointense area with focal hyperintensity, T2 and FLAIR- hyperintensity	Systemic Lymphoma	B-cell	Refuse treatment	ND	ND	Negative	Died
9	Kameda <i>et al.</i> ²⁷	96/M	Progressing gait disturbance and appetite loss	ND	Lt. Fr	T2- hypointense and by contrast enhancement	Primary CNS lymphoma	B-cell	Left frontal craniotomy	ND	ND	Negative	Died

F = female; M = male; Lt. =left; Fr= frontal; T= temporal; P= parietal; CNS= central nervous system; ND=not described; FLAIR= fluid-attenuated inversion recovery; VEGF= vascular endothelial growth factor

in the temporal lobe, parietofrontal subdura, and temporoparietal lobe. Most bleeding was intraparenchymal, and patients' presentation varied. In our case, the hemorrhage was located in the right temporoparietal lobe.

Intracranial hemorrhage is a common emergency in patients with brain cancer, with an incidence estimated at 2.4%.¹⁸ Intratumoral hemorrhage and coagulopathy are the main cause of intracranial hemorrhage.¹¹ Lung metastatic brain tumors hemorrhage is due to blood vessel invasion, neoangiogenesis, and tumor cell necrosis.¹⁹ Hemorrhage in primary glioblastoma multiforme is caused by highly invasive tumor cells.¹⁹ In our patient, coagulopathy was normal. The mechanisms responsible for the hemorrhage of CNS lymphoma are unknown, as published reports are scarce.

In conclusion, CNS involvement may occur in gastrointestinal lymphoma and may occur due to the inadequate initial treatment. Physicians should consider the possibility of metastatic CNS lymphoma in patients with intracerebral hemorrhage who have a history of gastrointestinal lymphoma presenting with neurological disturbances.

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DISCLOSURE

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Conflict of interest: None

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