

Solitary Primary Central Nervous System Plasmablastic Lymphoma in a Young Immunocompetent Female: Report on an Extremely Rare Entity with Review of Literature

Abstract

Primary central nervous system (CNS) plasmablastic lymphoma (PBL) in immunocompetent patients is an extremely rare disease, and only three cases had been reported till date. We present a case of a young female of age 21 years immunocompetent human immunodeficiency virus (HIV) and Epstein–Barr virus (EBV) negative, presented to us with left frontal lesion with weakness of the right upper and lower limbs for 9 months. Magnetic resonance images showed ring-enhancing lesions resembling a cavernoma or tuberculoma. Histopathological diagnosis was PBL. Surgical excision of tumor, followed by rapid recurrence with bleed in 3-month duration, was treated by adjuvant chemoradiotherapy. We report a young immunocompetent, HIV-negative, and EBV-negative female, with rapidly progressive primary CNS solitary PBL in the posterior frontal region, developed rapid recurrence of the tumor twice despite gross total excision.

Keywords: Chemoradiotherapy, immunohistochemistry, plasmablastic lymphoma, recurrence

Introduction

Plasmablastic lymphoma (PBL) is defined by the World Health Organization as a form of diffuse large B-cell non-Hodgkin's lymphoma (NHL), characterized by plasma cell differentiation and immunoblastic morphology. Human immunodeficiency virus (HIV) and Epstein–Barr virus (EBV), both, are known to cause an unusual surge in plasmablast levels in the blood and lymph nodes. PBL is an aggressive form of NHL occurring in the oral cavity of HIV-positive and EBV-positive cases. Other unusual sites are gastrointestinal tract, omentum, lung, nasal and paranasal regions, testes, bones, soft tissue, lymph nodes, bone marrow, and skin.^[1,2] PBL is primarily a disease of adults, wherein the male/female ratio is 5.7:1 for the oral type and 4:1 for the extraoral type.^[1] Only few cases of PBL in HIV-negative individuals have been reported till date. The incidence of PBL is 5% of all HIV-positive NHL, but the incidence in HIV-negative individual is unclear.^[1] Here, we report a young immunocompetent, HIV-negative, and EBV-negative female, with rapidly progressive primary central nervous

system (CNS) solitary PBL in the posterior frontal region. She underwent complete excision of the tumor, followed by rapid recurrence. To the best of our knowledge, this is the seventh case of primary CNS PBL and the third reported case of PBL in HIV- and EBV-negative individual.

Case Report

A 21-year-old female, resident of Indore, India, presented with complaints of frequent episodes of partial sensory seizures with paresthesias of the right upper and lower limbs on and off for 1 year and mild headache for 1 year. She had no history of drug addiction and no significant family history. Initially, seizure was controlled by antiepileptics. Magnetic resonance imaging (MRI) of the brain revealed small irregular lesion in the left posterior frontal region with cortical hyperintensity on flair images, more gyral distribution, and ill-defined diffuse enhancement on contrast without white-matter edema [Figure 1a]. Radiological differential diagnosis were demyelination disorders/tuberculoma or benign space occupying lesions like Dysembryoplastic neuroepithelial tumour or ganglioglioma. Due to the suspicion of

**Iqbal Mohd,
Sanjog Shankar
Gajbhiye,
Ritu Verma¹,
Jayesh Sardhara**

Departments of Neurosurgery and ¹Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Address for correspondence:

*Dr. Jayesh Sardhara,
Department of Neurosurgery,
Sanjay Gandhi Postgraduate
Institute of Medical Sciences,
Lucknow - 226 014,
Uttar Pradesh, India.
E-mail: jayeshsardhara83@
gmail.com*

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tuberculoma, anti-tubercular treatment was started. For initial 7–8 months, she remained asymptomatic. Gradually, she developed weakness in the right upper and lower limbs with a few episodes of focal motor seizures. On the second visit, in MRI, the lesion was heterogeneous intensity both in T1-, T2-weighted images with susceptibility-weighted angiography images showing blooming, resembling cavernoma [Figure 1b]. The patient was advised definitive surgery for tumor removal and seizure control. In the preoperative period, she presented in our emergency department with rapidly progressive right hemiparesis, headache, and vomiting. Radiological evaluation revealed significant enlargement of the posterior frontal lesion with evidence of hematoma in the lesion [Figure 1c]. On neurological assessment, she was conscious and oriented, with a dysphasic speech. Pupils were symmetrical and normally reacting to the light, vision was normal, and the right upper motor neuron facial palsy was present. Tone was increased in the right upper and lower limbs. Power

was 3/5 in the right upper and lower limbs; right-hand grip was 70% as compared to left grip. Deep tendon reflexes were exaggerated on the right side and normal on the left side. Plantar reflex was extensor on the right side. The sensory system was intact on both sides. There was no evidence of lymphadenopathy.

Systemic investigations

Her total leukocyte count was 1300/mm³ and differential counts included neutrophil-80; lymphocyte-15; eosinophil-1; and monocyte-4. Platelets count was 5 lakhs/mm³. Peripheral blood smear shows mildly reduced red cell mass with predominantly normocytic red cells and few macrocytes. Bone marrow aspirate showed no evidence of infiltration, excess blast, significant dyspoiesis, or hemoparasite. No evidence of lymphomatous infiltration. Serum electrophoresis with absolute quantification of M band: No M band in the gamma region was seen. Serum kappa-free light chain was 19.4 mg/l (3.3–19.4).

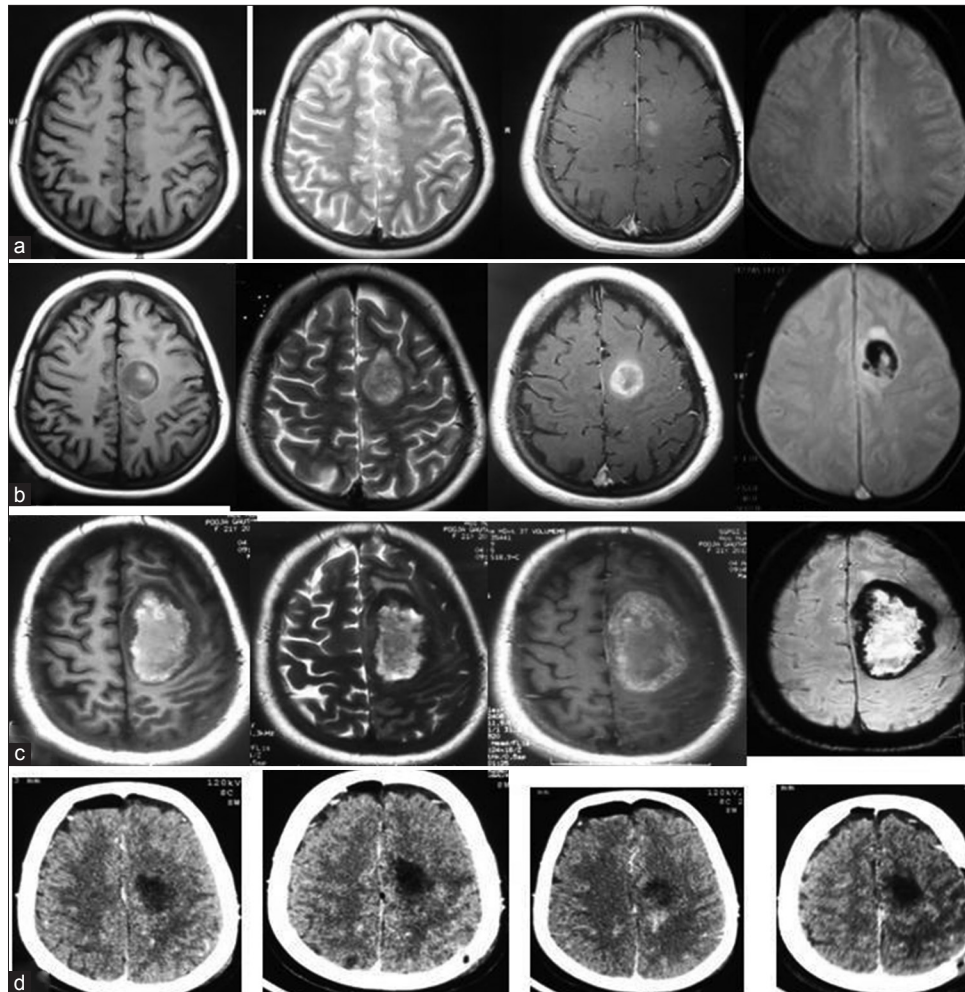


Figure 1: Serial magnetic resonance imaging reflects rapid progression of lesion due to recurrent bleeding in the tumor. During the first visit, patients presented with seizure; magnetic resonance imaging brain revealed small irregular lesion in left posterior frontal region with cortical hyperintensity on flair images, more gyral distribution, and ill-defined diffuse enhancement on contrast without white matter edema (a). On the second visit, in magnetic resonance imaging, lesion has appeared with heterogeneous intensity both in T1- and T2-weighted images with susceptibility-weighted angiography images showing blooming, which gives differential more toward cavernoma (b). (c) Showing significant enlargement of the posterior frontal lesion with evidence of hematoma in the lesion. Postoperative contrast-enhanced computed tomography suggested gross total excision of the lesion (d)

Cerebrospinal fluid (CSF) analysis was also negative for the malignant cells. IgM ELISA for HIV and EBV were negative. Fluorodeoxyglucose positron-emission tomography scan revealed a ring-enhancing soft-tissue thickening in the left frontotemporal region measuring 4.3 cm × 6 cm × 5.4 cm with central fluid attenuation. The lesion showed a significant mass effect on the surrounding structure, leading to the effacement of sulci, gyri with midline shift of 6 mm. Rest of the brain parenchyma and body showed normal tracer uptake.

Surgical treatment and outcome

The patient underwent posterior frontal craniotomy and complete excision of the lesion under ultrasound guidance [Figures 1d and 2]. Intraoperatively, the lesion had a firm, capsulated with evidence of hematoma in the premotor area. Capsule was dissected all over from parenchyma and excised, suggestive of cavernoma. Intraoperative ultrasound was used for accurately localizing the extent of the lesion and ensuring complete removal of the tumor. Postoperative contrast-enhanced computed tomography (CT) of the head revealed complete removal of the tumor. Postoperatively, hemiparesis also improved. The patient was discharged on day 7. Two weeks after

surgery, she again presented with a severe headache and right side hemiplegia. Noncontrast CT revealed left-sided posterior frontal hematoma at the previous surgical site with midline shift, which was suggestive of a tumor rebleed [Figure 3]. There was no coagulopathy on laboratory investigations. She underwent resurgery for hematoma evacuation. Intraoperatively, a well-defined hematoma with an organized capsule around the lesion was found. Intraoperative impression was of a cavernoma. Gross total excision was done. Postoperatively, hemiplegia persisted. Histopathology report was suggestive of PBL. The patient was registered and transferred for adjuvant chemoradiotherapy. The patient received treatment as per the DEANGELIS protocol of chemoradiotherapy. The patient ultimately succumbed to her illness after 8 months of diagnosis.

Histopathological findings

Section showed a tumor comprised diffuse sheets of large atypical cells. The atypical cells were plasmacytoid in appearance having eccentrically placed round nuclei, coarse chromatin, prominent nucleoli, and a moderate amount of eosinophilic cytoplasm. Many mitotic figures and areas of necrosis were observed. Tumor cells invading adjacent normal brain parenchyma and blood vessels.

Immunohistochemistry

Tumor cells were focally positive for leukocyte common antigen (LCA) and strongly positive for CD138 and vimentin and negative for CD20, PAX-5, CD3, CD30, BCL-2, cytokeratin, synaptophysin, CD99, and desmin. Ki-67 index was 50% [Figure 4].

Adjuvant chemoradiotherapy

The patient had received chemoradiotherapy in “DEANGELIS” protocol. In this protocol, Intravenous methotrexate, vincristine and procarbazine were administered in 1st, 3rd, 5th, 7th and 9th week of radiotherapy. Intrathecal methotrexate was administered in 2nd, 4th, 6th and 8th week. Whole brain radiation therapy was given from 13th to 17th week. Intravenous high dose cytarabine b administered in the 18th week. After the completion of chemoradiotherapy in the last follow-up (36 week after surgery), clinically, the patient was conscious, oriented,

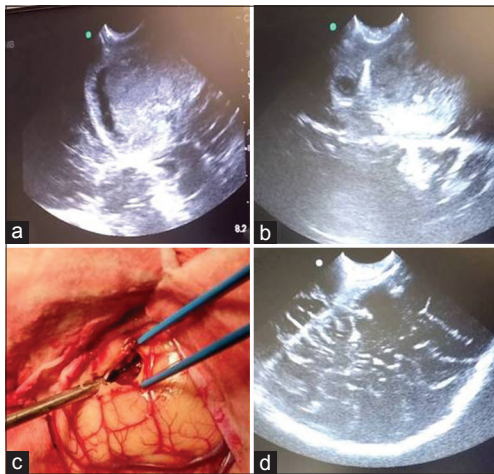


Figure 2: (a and b) Hyperechogenic lesion noted intraoperatively using a USG. (c) Intraoperative image after resection of the tumour through the transcortical corridor. (d) Post excision, there is no hyperechogenic shadow suggestive of complete excision of the tumour

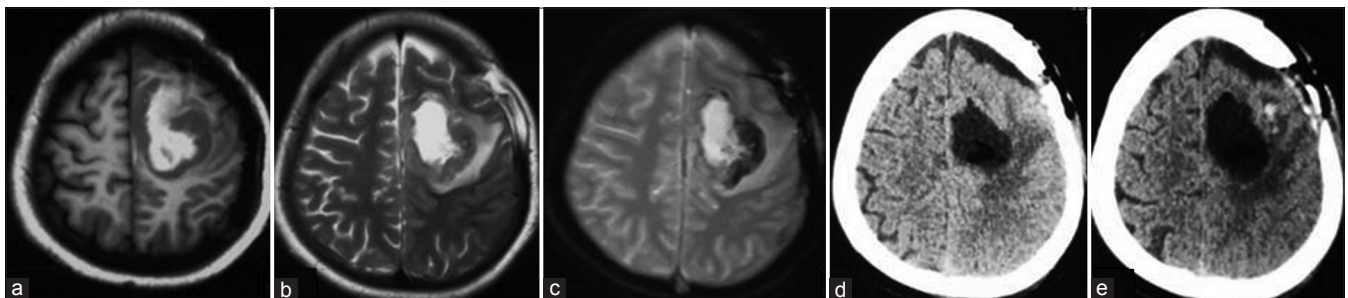


Figure 3: (a,b and c) MRI head in the post operative period (2 weeks) when patient presented with sudden onset right hemiplegia and severe headache shows rebleed at the operative site s/o tumoural rebleed. (d and e) Post operative NCCT head showing complete hematoma evacuation

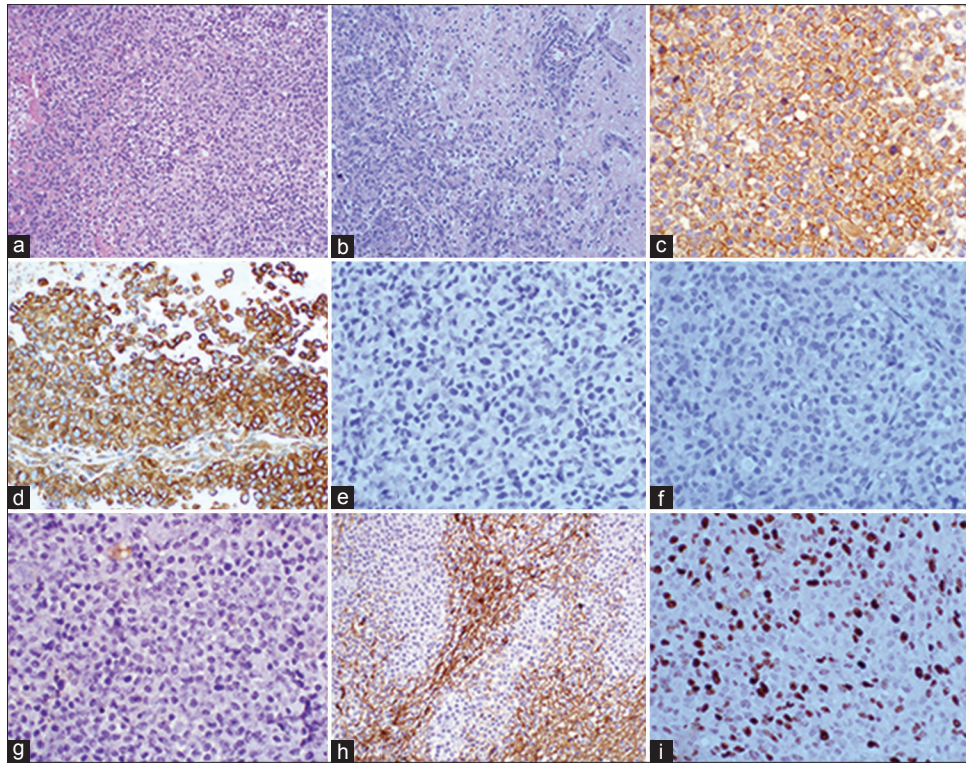


Figure 4: Diffuse sheets of plasmablasts, characterized by large cells with large eccentric nuclei, prominent central nucleoli, and a moderate amount of eosinophilic cytoplasm (a). Tumor is invading the adjacent brain parenchyma (b). Tumor cells are immunoreactive for CD138 (c), vimentin (d) and are negative for CD20 (e), CD99 (f), Bcl2 (g), GFAP (h). Ki67 index was 50% (i)

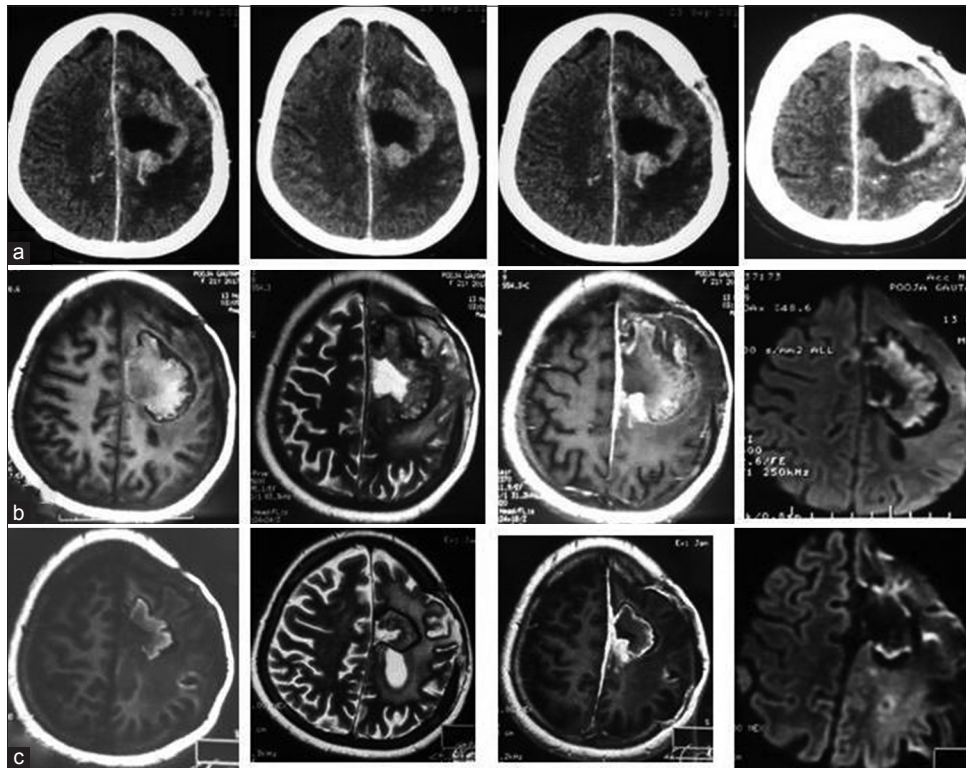


Figure 5: (a) Lesion prior to beginning Chemoradiotherapy. (b) Decrease in size of tumour during 7th week of chemoradiotherapy. (c) More than 50% decrease in size of the tumour on completion of chemoradiotherapy

and right hemiparesis improved to power 3/5, no episode of seizure after surgery. In serial radiologically, MRI

evaluation was suggestive of a reduction in tumor size compared to prechemoradiotherapy status [Figure 5].

Discussion

Primary CNS lymphoma accounts for 2% of CNS malignancies.^[3] PBL is an aggressive subtype of B-cell lymphoma with a poor prognosis. PBL of CNS is very rare, and only handful of cases of PBL have been reported till date.^[4-10] PBL mostly occurs in HIV, EBV, and immunodeficient individual predominantly in males. Our case is a young immunocompetent female with HIV- and EBV-negative status. PBL is characterized by a cellular proliferation of pleomorphic plasmablastic cells with eccentrically located nuclei.^[10] Apoptotic bodies, single-cell necrosis, tingible macrophages, lymphoglandular bodies, cytoplasmic vacuoles, and background necrosis can sometimes be seen as additional pathological characteristics. CD38, CD138, and MUM-1 with negativity or weakly positive B-cell lineage marker (LCA/CD45, CD20, and PAX-5) are characteristic immunophenotypic marker of PBL.^[10] It should be morphologically distinguished with anaplastic or plasmablastic plasma-cell myeloma, immunoblastic cell type diffuse large B-cell lymphoma, anaplastic diffuse large B-cell lymphoma, ALK-positive large B-cell lymphoma, and HHV8-related origin of Castleman's disease. Characteristic diagnostic features of PBL are clinical history (immunocompromised status), disease site (predominantly parenchymal – frontal or parietal cortex), tumor cell phenotype, high proliferation index, and EBER *in situ* hybridization.

Our case was diagnosed as cavernoma radiologically and as per the intraoperative impression but turned out to PBL on histopathology. Ahn SJ *et al.* studied the apparent diffusion coefficient method to differentiate between primary cerebral lymphoma and glioblastoma and concluded that analog-to-digital conversion mean from the whole tumor volume may be helpful in distinguishing lymphoma and Glioblastoma.^[3] Urrego *et al.* evaluated CSF cytology along with flow cytometry, radiology, and histology and emphasized that clinical and radiological correlations should be done for early diagnosis, and while doing CSF cytology, this entity should be considered if neoplastic cells are seen.^[4] In PBL, clonal IgH chain and MYC gene rearrangement is seen, especially in EBV-positive patients.^[5] CNS PBL is characterized by a high rate of relapse rate and death. A standard therapy has not yet been described in the sparse literature available on CNS PBL. Treatment usually consists of surgical resection of lesion (if single lesion or one of the multiple lesions producing a mass effect and raised intracranial pressure, or to take a biopsy for histopathological diagnosis), followed by chemoradiotherapy. Various chemotherapy regimens include cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), R-CHOP, and cyclophosphamide, vincristine, doxorubicin, and high-dose cytarabine (CODOX-M/IVAC). Novel agents used in myeloma therapy are currently applied to PBL considering that PBL shares many morphologic and immunophenotypic characters with plasmablastic myelomas. One of the newly

emerged therapeutic options for PBL is bortezomib, which is a proteasome inhibitor and a cornerstone in myeloma therapy and relapsed or refractory mantle cell lymphoma. Bortezomib represents a new therapeutic option for PBL. Bibas *et al.* have used bortezomib alone or in combination with chemotherapy in patients with PBL, and they reported that the results were promising but failed to show any survival advantage over standard chemotherapy. An ongoing study is evaluating the therapeutic value of autologous EBV-specific chimeric antigen receptor (CAR) T-cells with CD30 as the target. Potentially, CAR T-cells can be directed against EBV antigens in patients with EBV-associated lymphomas including PBL.^[11] PBL with CNS involvement either primary or secondary carries poor prognosis with short survival of 3 days to 6 months.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/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 due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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