

PRIMARY CENTRAL NERVOUS SYSTEM T- CELL LYMPHOMA OF THE BRAIN IN AN IMMUNOCOMPETENT PATIENT

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ABSTRACT:

Primary central nervous system (PCNS) T-cell lymphoma is a rare disease and rarer if it is seen in immunocompetent patients. The PCNS lymphoma makes up 1-7% of primary brain tumors. PCNS T-cell lymphoma accounts for about 2% of all PCNS lymphoma and almost 99% are seen in immunocompromised patients (Latta et al 2010, Batchelor et al 2003). Here, we report a case of PCNS T-cell lymphoma in an elderly patient who is immunocompetent. The radiological findings, histopathological studies, and reviews of the current literature of this rare condition are discussed.

CASE REPORT:

A 65-year-old man presented with a one-month history of slurred speech, drooling of saliva, right side facial weakness with progressive weakness, and numbness of right upper and lower limbs. He gave no significant past medical illness.

He was extensively investigated at the private medical center in which a contrast enhanced Computed Tomography (CECT) scan of the brain was done that showed extensive white matter edema at the left fronto-parietal lobes with relative sparing of the cortical grey matter. However, there was no obvious enhancing

lesion within it (figure 1). He was further investigated with magnetic resonance imaging (MRI) study of the brain with administration of gadolinium which demonstrated an ill-defined irregular inhomogeneous enhancing white matter mass at the left fronto-parietal lobes. Presence of extensive infiltrative vasogenic surrounding white matter edema, confined to the left fronto-parietal lobes without crossing the midline to suggest contralateral infiltration. There was mild compression of the ipsilateral lateral ventricle with minimal midline shift to the right. Regular nodular thickened

leptomeningeal enhancement noted at its periphery. No central necrosis or intratumoral hemorrhage (Figure 2 and figure 3).

In view of age at presentation without extra-cranial primary lesion, primary central nervous system tumors such as high-grade astrocytoma (glioblastoma), high-grade oligodendrocytoma, or primary CNS lymphoma were considered with differential diagnosis of solitary brain metastasis. He was then referred to University Malaya Medical Centre for further management.

Baseline blood laboratory investigations were within normal limits. HIV and hepatitis screen were negative and CD4 count was within normal limits. Central nervous system examinations revealed right facial nerve palsy (upper motor neuron), slurred speech, brisk reflexes, and right hemiparesis (power of 4/5). No primary lesion detected on contrast enhanced computed tomography scans of the thorax, abdomen, and pelvis (TAP).

The plan was to perform an excisional biopsy of the left frontal lobe lesion. Thus, routine image guided surgery (IGS) imaging of the brain, CT, and MRI were repeated prior to surgery. He subsequently underwent craniotomy and excision biopsy of the left frontal lobe mass under general anesthesia. Intraoperative and immediate post-operative phases were uneventful. A few days after the biopsy, his speech and right-side limbs weakness have improved significantly as well as resolution of the right facial nerve palsy; probably due to reduced edema and mass effect.

Histopathology examination (HPE) showed large lymphoid cells of T-cell phenotype with irregular vesicular nuclei, clump chromatin, and prominent nucleoli. The immunohistochemical staining of the tumor cells exhibited strong immunoreactivity to CD3 which confirms the diagnosis of non-Hodgkin lymphoma of T-cell phenotype (Figure 4). Due to

limitation of the availability of the stains, other additional stains were not performed. Following discussion with the patient and his family members, the patient was treated with high dose intravenous methotrexate and was discharged home with oral dexamethasone as maintenance.

DISCUSSION

Lymphoma is a tumor of the lymph cells that forms our body's immune system. Primary central nervous system lymphoma (PCNSL) is the extra-nodal form of the non-Hodgkin lymphoma that primarily starts in the central nervous system. The PCNSL makes up 1-7% of primary brain tumors in which 90% of central nervous system (CNS) lymphoma are supratentorial in location (Latta et al 2010, Batchelor et al 2003). It could be well circumscribed or infiltrative in pattern. PCNSL are usually presented with multiple lesions, only occasionally solitary. The lesion may have areas of central necrosis and internal hemorrhage especially in immunocompromised (HIV) patients. The prevalence of T-cell PCNSL was reported to be higher in East Asian countries – such as Korea (16%) and Japan (8-14%) – as compared to European and other Western countries – such as France (3.6%) and United States (2%) (Shenkier et al 2005, Behbahani and Lyons, 2011).

The main symptoms of PCNSL lymphoma caused by raised intracranial pressure from blockage of the ventricles leading to obstructive hydrocephalus resulting from build-up of cerebrospinal fluid (CSF) production or poor out flow from direct compressive pressure. Clinical presentation includes vomiting, headache, and diplopia. Other neurological symptoms are hemiparesis, loss of coordination, imbalance, seizure, and neuropsychiatric disturbances. The natural progression of the disease is usually dramatic with short-live response to steroid and radiotherapy (Batchelor et al 2003, Osborn et al 2015, Behbahani and Lyons 2011). Favorable prognostic factors which increase the median survival rate are single lesion,

absence of meningeal or periventricular infiltrations, and an immunocompetent patient of less than 60 years of age at presentation. On the other hand, elevated lactate dehydrogenase enzyme (LDH) and CSF protein levels are poor prognostic indicators. PCNSL is a disease in which the prognosis is much poorer than most other localized extra nodal lymphomas of indistinguishable histology (Ponomaryov et al 2014, Kim et al 2013, Bhagavathi and Wilson 2008).

In general, the most common primary brain tumor in an adult and elderly is Glioblastoma multiforme (GBM). It's associated with IDH1 and IDH2 mutations. Common site is the subcortical and deep periventricular white matter region and easily spread across the white matter tract along the corpus callosum and spinal cortical tract. On MRI T1W, its poorly marginated, on T2W/Flair shows heterogenous hyperintense with extensive perilesional edema. Post contrast T1, its shows irregular rim enhancement with central non-enhancing of necrotic core (Osborn A. G. 2015).

Advanced MRI techniques such as Dynamic Susceptibility Contrast (DSC) MR perfusion and MR Spectroscopy may provide additional valuable information about the lesion, unfortunately, due to limitations in our setting, including cost considerations, availability of these advanced imaging techniques, and patient condition, we did not perform these in our patient.

Histopathology presentation of PCNSL is typically a collection of atypical lymphocytes within the parenchyma of the brain. It also may be seen in the eye, spinal cord, or as leptomeningeal involvement (Han,2017). A large percentage of PCNSL cases are of the diffuse large B-cell phenotype, followed by T-cell phenotype, Burkitt, lymphoblastic and low-grade lymphoma. The lack of systemic manifestation is one of the main diagnostic criteria.

T-cell lymphoma is a rare phenotype in, approximately 2% to 9% of all cases of PCNSL. Under low power microscopy, perivascular cuffing is commonly seen, along with the spillage to the surrounding tissue, forming diffuse pattern. The cells are typically intermediate to small, with irregular nuclear membrane. In some case the features of atypia is minimal, especially in young patients (Gianni, 2014) and its diagnosis is reserved by the expression of monoclonality in the immunohistochemistry.

Apart from the monoclonal expression of CD3 (a common T lymphocyte marker), the tumor cells also express other common T-cell markers such as CD4 (T-helper phenotype), CD8 (cytotoxic phenotype) as well as the alpha/beta chains (common) and gamma/beta chains (rare). A definitive diagnosis in a reference center usually made with the aid of polymerase chain reaction (PCR) technique that detects the T-cell receptor (TCR) gene clonal rearrangement (Gianni,2014).

PCNS T-cell lymphoma has remained a very rare entity despite the gradual increase in global incidence, due to growing numbers in immunocompromised population which results from an increase in prevalence of Acquired Immunodeficiency (AIDs) virus infection, organ transplant and an aging population (Batchelor et al 2003). In the advance of antiviral therapy, the incidence of T-cell PCNSL has shown a decreasing trend. However, the incidence of T-cell PCNSL in immunocompetent individuals continues to increase and remains unexplained. In the extensive studies done by Ferreri (2003) and Guan et al (2011) did not reveal any male or infratentorial preponderance; however, all the tumors which originate from superficial subcortical area raises the possibility of the pathogenesis being of T-cell PCNSL which differs from those of diffuse large B-cell lymphoma. MRI analysis of PCNSL T-cell phenotype

showed predilection for subcortical location and associated with high incidence of intra-tumoral hemorrhage, peripheral rim enhancement, and cystic areas that are consistent with necrosis (Erdag et al 2001). In a recent retrospective study of PCNSL T-cell phenotype by Shenkier et al (2005); in 45 patients, 28% of the tumors showed angiocentric appearance, 48% were small or "small to medium", and 6% showed pleomorphism. They also found that the presentation of T-cell PCNSL varied between the immunocompetent and immunocompromised population. Those who were immunocompromised, particularly due to AIDS, had shown predilection for infra-tentorial location of tumors as compared with other diseases. Multiple lesions were more commonly seen in immunocompromised patients while immunocompetent populations presented with single lesions. The researchers emphasized that PCNSL T-cell is usually presented with cystic degeneration with necrosis and hemorrhage, while histopathological appearance was as described above. There is no definite pattern of PCNSL T-cell emergence clinically, radiologically, and pathologically (Shenkier et al 2005). Optimal treatment regime for T-cell PCNSL continues to evolve. An excellent study by Shenkier and colleagues have concluded that in terms of presentation and prognosis, both B-cell and T-cell are similar and have a better outcome with methotrexate even through the varied modes of drug delivery; intravenously, intra-arterially, or intrathecally. Some of these patients also received concurrent radiotherapy (Rubenstein et al 2006, Guan et al 2011, Shenkier et al 2005). Levin et al (2008), reported that a high dose of methotrexate with procarbazine and lomustine in combination with cytarabine had shown a median survival of 16 months in four patients and 36 months for one patient. It appears that treatment with methotrexate may provide better survival in T-cell PCNSL. It has also been reported

that radiation and corticosteroids have shown complete response in 20-50% of patients with a median survival of 13.5 months (Levin et al 2008, Da Silva et al 2006). Having said all this, the overall prognosis of T-cell PCNSL still remains significantly controversial and without a consensus with some reports showing poor prognosis while others have reported better overall survival time.

CONCLUSION

T-cell PCNSL is rare especially in the immunocompetent. More studies are required to understand the pathophysiology and prognosis of this tumor within the immunocompetent to help improve the diagnosis, treatment and prognosis in this type of lymphoma.

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FIGURE LEGENDS:

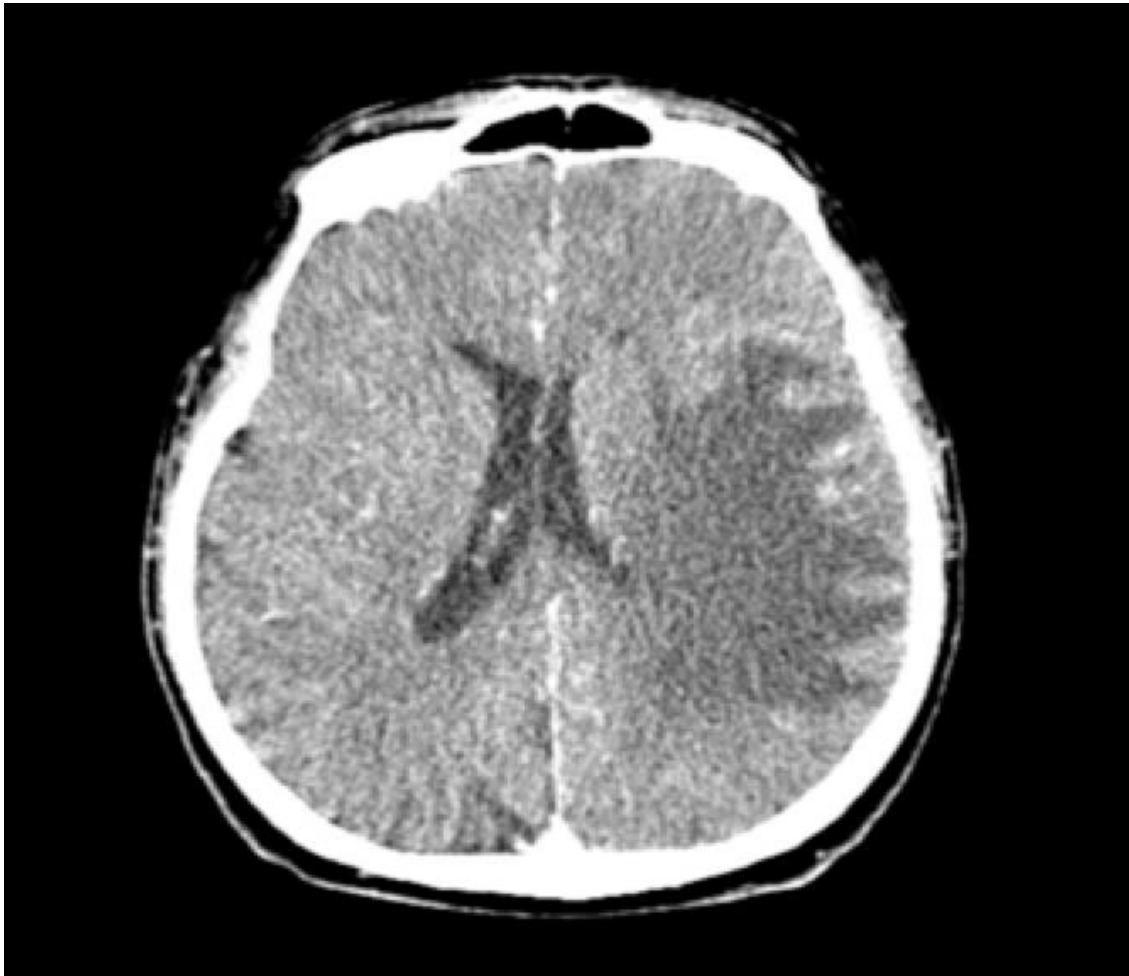


Figure 1: An axial image of contrast enhanced computed tomography scan of the brain shows subcortical and deep white matter oedema of the left fronto-parietal lobes sparing the cortical grey matter. No obvious enhancing mass. Minimal regular thickened leptomeningeal enhancement present at its periphery.

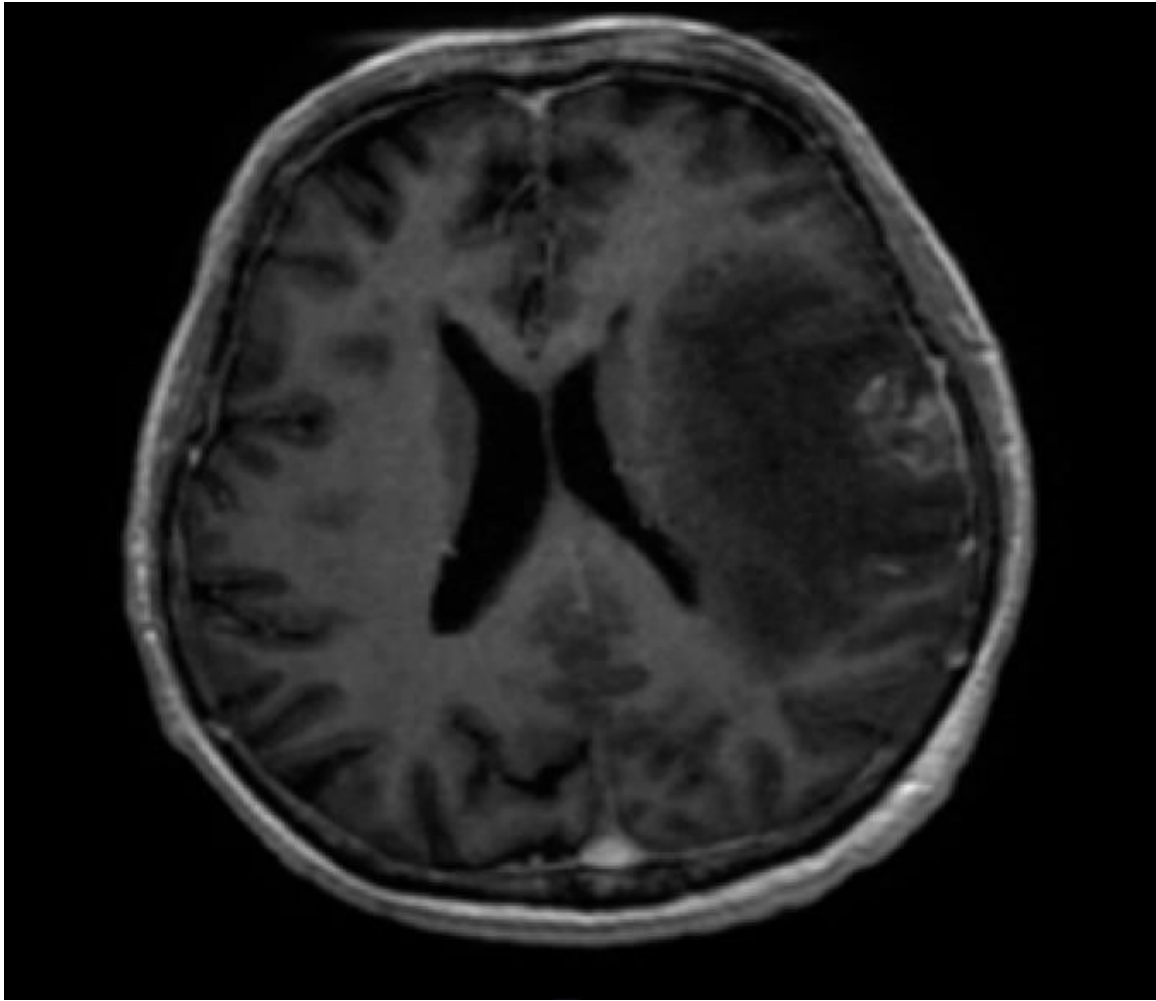


Figure 2: MRI of the brain, T1W post gadolinium, on axial plane at the level of lateral ventricle shows solitary inhomogeneous enhancing mass at the left frontal lobe with marked perilesional edema causing mass effect compressing onto the ipsilateral lateral ventricle. Thick irregular nodular leptomeningeal enhancement of the adjacent meninges present.

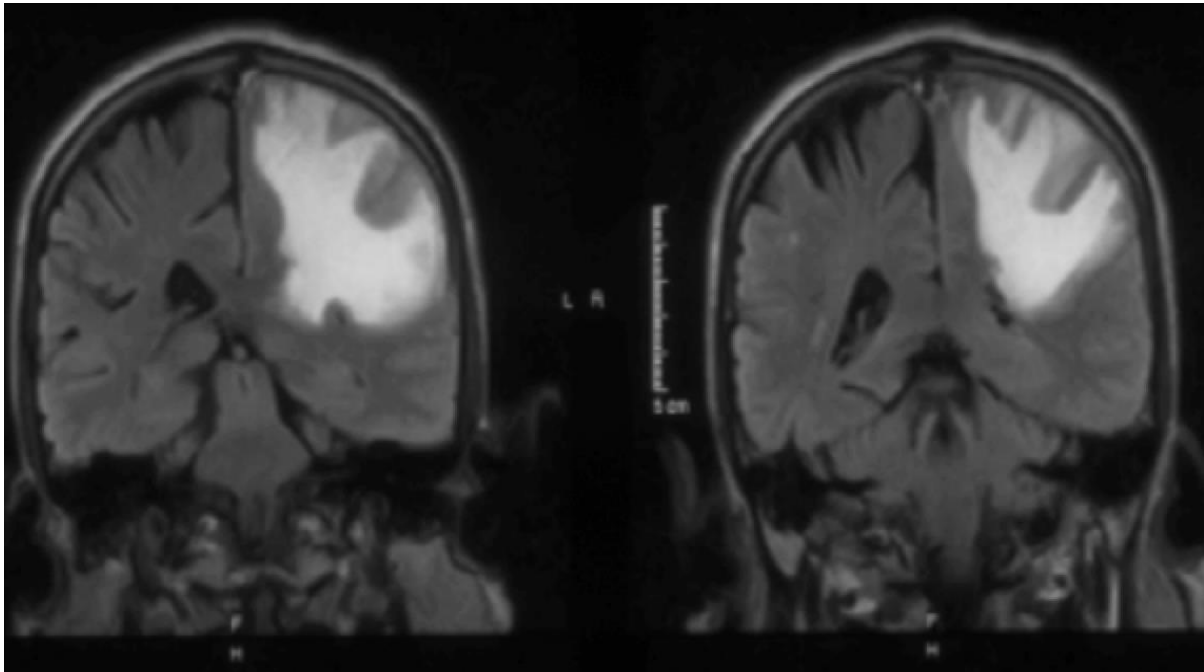


Figure 3: MRI on coronal plane of FLAIR sequence, showed extensive infiltrative edema within the superficial and deep white matter tract of the left fronto-parietal lobes involving the genu and body of the left corpus callosum compressing onto the ipsilateral lateral ventricle without crossing the midline. Cortical grey matter swelling noted as evident by effacement of the sulci and gyri.

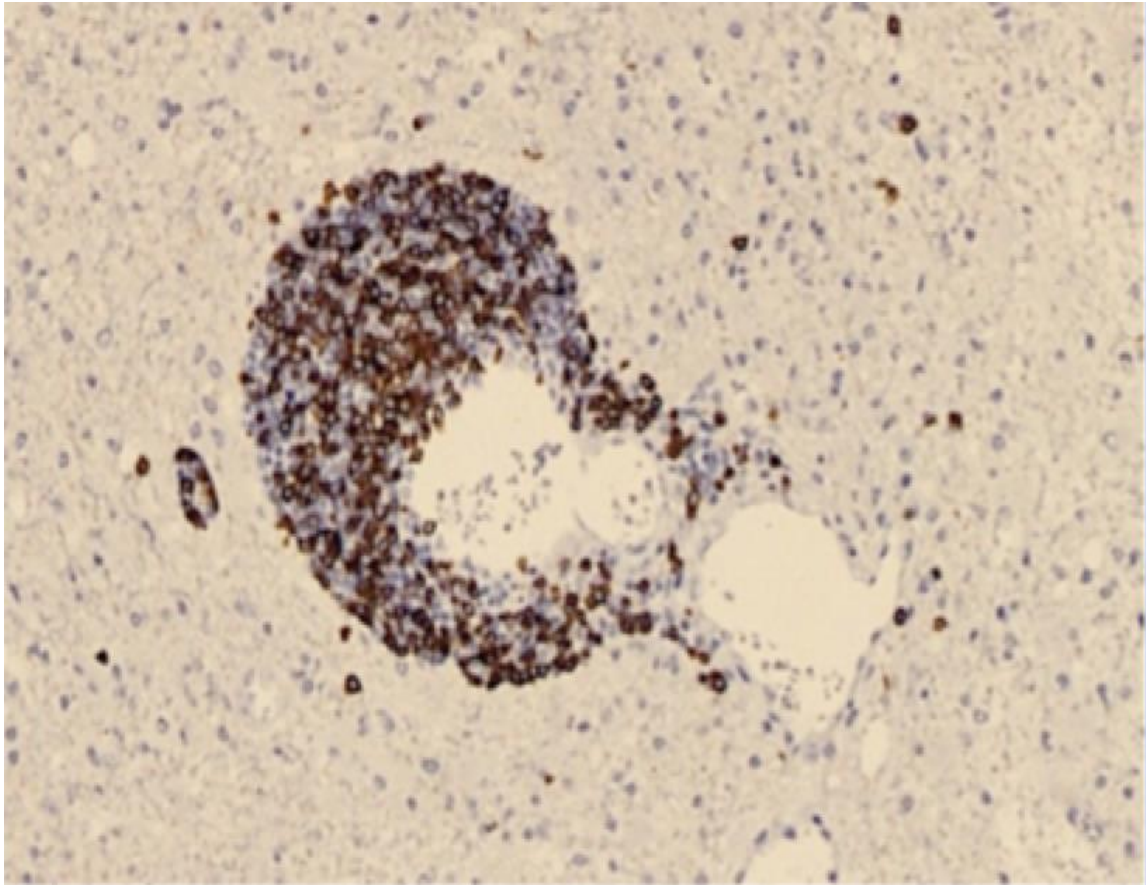


Figure 4: Photomicrograph showing brain tissue with dense perivascular cuffing by immature lymphoid cells which are strongly immunopositive for CD3. Immunoperoxidase stain for CD3 X 200.