PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL) TYPE DIFFUSE LARGE B CELL IN IMMUNOCOMPETENT PATIENT: A CASE REPORT

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ABSTRACT Primary central nervous system lymphoma (PCNSL) is characterized as an extra-nodal non-Hodgkin lymphoma, which is a rare type of brain tumor. PCNSL often happens in an immunocompromised patient and rarely showed in an immunocompetent patient. This is a case of a 63-year-old man with a supratentorial tumor who first suspected as high-grade astrocytoma and underwent resection for his tumor, and the result showed PCNSL with diffuse large B Cell in histopathology. The patient was then admitted to the neurology department for general weakness and mass in his forehead. CT scan and MRI brain examinations revealed a relapsed tumor in his left fronto-temporo-parietal lobe that was surrounded by oedema and was enhancing after intravenous contrast administration. Histological and immunochemistry analysis of the resected specimen showed primary diffuse large B-cell lymphoma with CD20 positive. Radiation therapy was applied to the patient without chemotherapy, and at his last follow-up (after fifth radiation), the clinical appearance of the patient is better. The role of radiation probably should be reconsidered for PCNSL tumors.

KEYWORDS Diffuse large B-cell Lymphoma, Immunocompetent, Primary Central Nervous System Lymphoma (PCNSL), Radiotherapy

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare form of extranodular non-Hodgkin's lymphoma, where the incidence is estimated to be only 4% of the total incidence of primary brain tumors in the United States. [1,2] At the first PCNSL was described as a perithelial tissue sarcoma in the central nervous system, and then in 1974, PCNSL was known to originate from a lymphoma. PCNSL emerged in the fifth to seventh decade of life, and the incidence has increased in the last decade due to technological developments that contributed significantly to making the diagnosis early.[4] Most of the PCNSL (95%) is a diffuse large B-Cell Lymphomas (DLBCLs), where T-cell lymphoma is estimated that only contribute 1-3.6% of the total PCNSL.[5,6] DLBCLs are characterized as high grade, and most have a positive CD20, and can be found in the ocular region, spinal cord, and cerebrospinal fluid.[4] Supratentorial single lesions from PCNSL can be found in 60-70% of patients, with clinical manifestations such as headache, nausea, vomiting, seizures, impaired speech and vision, and focal neurological deficits.[4,7] Some investigations for the diagnosis of PCNSL such as computed tomography (CT) scan of the head, magnetic resonance imaging (MRI) of the head, microscopic ocular examination, cerebrospinal fluid analysis, and biopsy examination.[8] The PCNSL description of the biopsy results resembles the morphology of a glial tumor, especially oligodendroglioma. The incidence of these tumors is related to conditions of low immunity, such as organ transplants and HIV.[8] Chemotherapy is the main choice of PCNSL therapy, either with and without additional radiotherapy. Corticosteroids can be used as additional therapy, but surgery is not recommended for brain lymphoma and is only done in certain conditions.[8] PCNSL with diffuse large type B-cell lymphoma is a tumor that is very aggressive and generally has a poor prognosis, but about 1-3% of young adult patients have a better prognosis.[9]

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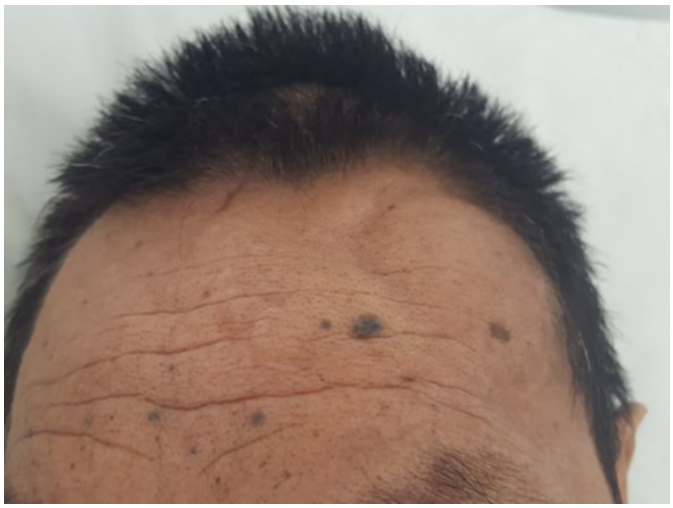

Figure 1: Bump on left forehead.

Case report

Male, aged 63 years old, HIV negative, right-handed, ethnic Balinese, came to the Neurology Polyclinic in Sanglah General Hospital in a state of decreased consciousness, tending to be sleepy, and complained of experiencing general weakness since two days before coming to the hospital. Patient appetite is also said, decreased due to inadequate contact. The patient also complained about the weakness of the right half of the body for two months before coming to the hospital, which initially was mild but worsened when he came to the hospital. The patient also complained of headaches for six months, which worsen in the last three months before admission. The patient is said to have begun to talk incoherently for one month, especially when the headache felt to be severe. Complaints of nausea and vomiting, tingling, history of fever, and previous trauma are absent. The patient had a history of seizures three months before admission. It was said when the seizure occurred, the patient's head turned to the left and then twitched throughout the body. Patients also complained there are bumps on the left side of the forehead for two months before admission, which is felt like throbbing and tense sensation. The bump was said to grow larger when the headache worsens, and the head is started to feel heavy and then followed by a decrease in consciousness (Figure 1). The patient is diagnosed with a brain tumor two months prior to admission, and has been suspected of high-grade gliomas and had undergone tumor resection. One month earlier, patients only complained of chronic progressive headaches and a history of seizures. Then one month after surgery, the patient started to feel weakness in the right half of the body, and the headache worsens. Then the patient was admitted to Sanglah General Hospital. The patient had a history of using phenytoin as an anticonvulsant and never had seizures until the day of admission. There was no tumor history in the patient's family. The patient previously worked as a farmer, and there was no history of smoking and alcohol consumption. The patient does not have a history of multiple sexual partners or drug use. There were no signs and symptoms of HIV infection in the patient.

From the clinical examination, we found that the patient had stable vital signs. The neurological examination revealed that the patient was somnolence, where the patient was only able to open his eyes when he was called, disoriented, and could only localize pain. Patients also had right supranuclear facial nerve paresis, right spastic hemiparesis with grade three in the upper limb and grade two in the lower limb, but no pathological reflexes were found. Head CT scan with and without contrast first conducted three months prior to admission (Figure 2) and found with a hyperdense lesion in the left fronto-temporoparietal lobe with surrounding perifocal edema. MRI of the head then performed to further evaluate the tumor (Figure 3) and obtained their single lesion in the left frontotemporal lobe which is suspected to be a high-grade astrocytoma with a diagnosis of high-grade gliomas. Based on these results, tumor resection was performed, and a histopathological examination was performed. When closing the location of the operation, the skull piece is not placed in its original place but on the top of the crown due to a swollen brain condition. Histopathological results showed a picture of a malignant round cell tumor with a differential diagnosis of malignant lymphoma (Figure 4). Then an immunohistochemical examination was carried out to confirm the results of the histopathology.

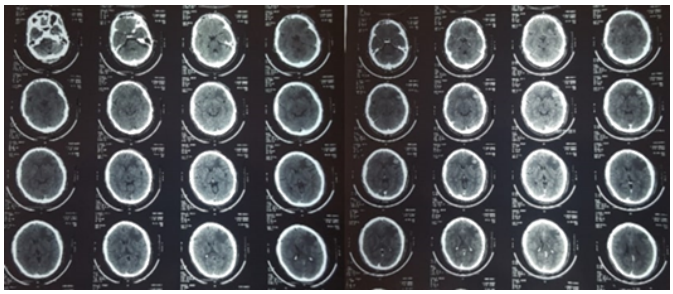

Figure 2: First head CT scan with and without contrast.

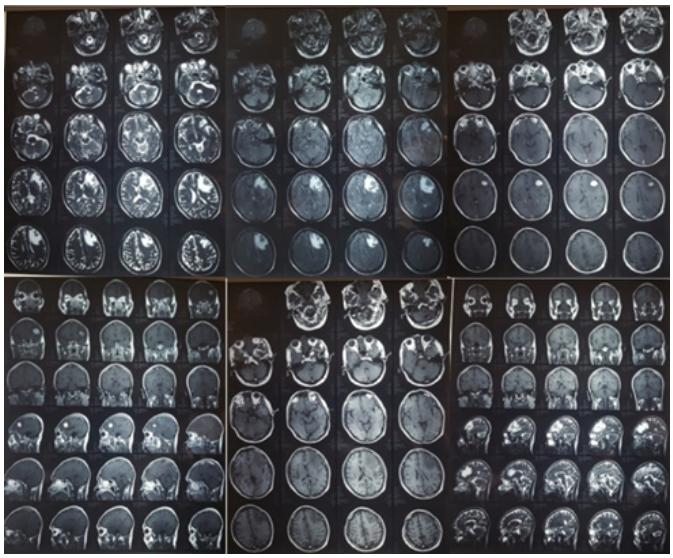

Figure 3: Pre-surgical head MRI with contrast.

The patient was allowed to go home two weeks after surgery in good condition without neurological deficits. Two weeks later, the patient begins to feel a sense of heaviness in his right hand and foot. MRI of the head with contrast and then carried back two months after surgery for further investigation and it was shown solid tumors with broad tentacles edema in the right temporoparietal region, causing a shift to the right side of the brain tissue (1.94 cm) and herniation to the left of sub-calvaria (Figure 5). Immunohistochemical results then show the results of diffuse large B-cell lymphoma with CD20 positive subtype non-germinal center B-cell like phenotype, which confirms the

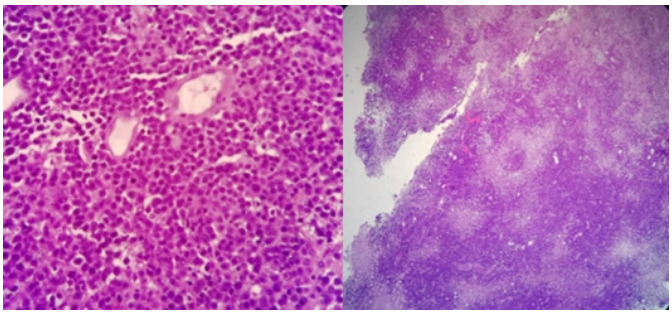

Figure 4: Histological analysis of tissue sample.

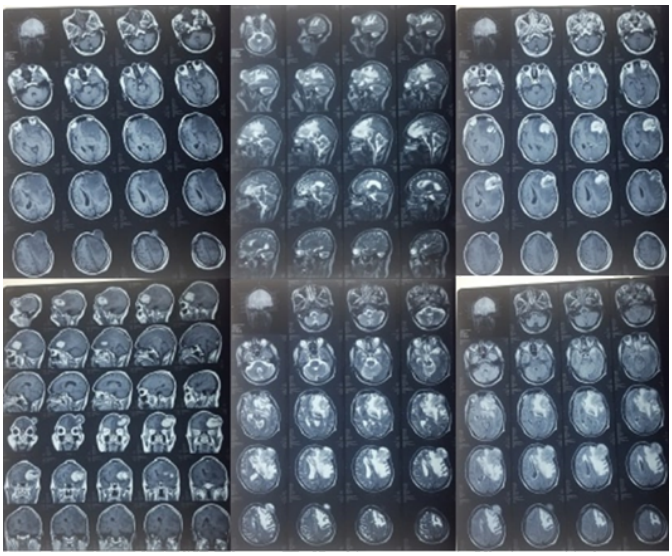

Figure 5: Post-surgical head MRI with contrast.

diagnosis in the direction of a lymphoma. Upper and lower abdominal ultrasounds were performed to determine the stage, and there were no pathological signs, so this confirmed that this is a PCNSL.

After the establishment of the diagnosis PCSNL based on the results of immunohistochemistry, patients then underwent whole-brain radiotherapy as many as 25 times in outpatient care, but one month later, the patient readmitted to hospital with a clinical bump on the head that got bigger accompanied by a decrease in consciousness. Patients then died before repeat imaging investigation to see the progression of the mass of post-radiotherapy.

Discussion

PCNSL is defined as lymphoma that is limited to the spinal-cranial axis, where less than 5% of tumors originate in the cranium and the spinal cord.[8,10] PCNSL contributes to around 3% of intracranial neoplasms and 4-6% of extra-nodal lymphomas with an incidence of 0.5 cases per 100,000 people. More than 50% of PCNSL cases are found in the supratentorial area.[8,11] A risk factor for PCNSL is a state of compromised immunity, including HIV infection, patients on immunosuppressive therapy or immune-enhancing drugs.[12] A PCNSL event in immunocompetent patients can be associated with an ageing process of the immune system. PCNSL mostly diagnosed at the age of 45 to 70 years old with an average age of 60 years and the incidence of male versus female was 1.2-1.7 compared to 1,41.[12]

Diffuse large dominant B-cell lymphoma is found in PCNSL and is characterized by its aggressive nature.[12] More than 95% of patients with PCNSL are lymphomas originating from B-cells, but patients with central nervous system lymphoma originating from T-cells show no difference in outcomes based on a series of studies collected from 12 cancer study centers.[6]

The diagnosis of PCNSL is made 3-6 months after the onset of symptoms. The clinical manifestations of PCNSL are not typical, and focal neurological deficits are the most common manifestations of both motor and sensory deficits.[13,14] Other symptoms that can be found, such as neuropsychiatric symptoms, seizures, increased intracranial pressure, visual symptoms, vertigo, headaches, and dysarthria. Cranial, cerebellar, or brain stem disorders are rare.[14,15] Cognitive deficits, changes in consciousness, and psychomotor slowdown can be found in patients with PCNSL.[16] The differential diagnosis of PCNSL such as tumor metastases, gliomas and toxoplasmosis, and in some rare cases a PCNSL can have signs of demyelinating disease.[8]

In an immunocompetent PCNSL, solitary lesions were found in brain parenchyma in 66% of cases, in the cerebral hemisphere in 38% of cases, 16% in the thalamus or basal ganglia, 14% in the corpus callosum, 12% in periventricles, and 9% in regions of the cerebellum.[17] Intraocular involvement is found in 5-20% of patients and meningeal involvement in 16% of total patients, where isolated meningeal lymphoma is around 5% of all PCNSL.[18] Although MRI by contrast and CT scan are the modality of choice for diagnosing PCNSL, MRI and CT provide features that are not specific to a PCNSL. Imaging study findings in immunocompetent patients include relatively homogeneous lesions, isointense grey matter on MRI, and hyperdense on CT scan, and contrast sting is obtained. This finding is not specific enough to effectively diagnose PCNSL because high-grade glioma can also provide such characteristics.[19]

The pathology diagnosis approach consists of the immunohistochemical examination of brain biopsy tissue. Corticosteroids should not be given before biopsy because although corticosteroids can decrease peritumoral edema of the brain, corticosteroids can produce lymphocyte apoptosis and confound histological diagnosis.[18] Evaluation for staging must be established before confirming histopathology to exclude a systemic concomitant lymphoma. Complete physical evaluation and neurological examination, cognitive function assessment (MMSE), laboratory evaluation (determination of serum LDH, liver function, kidney function, HIV serology), lumbar puncture for cerebrospinal fluid cytology, CT scanning of the thorax/abdomen/pelvis, bone marrow biopsy, and ophthalmological examination with a slit lamp must be performed to diagnose a PCSNL.[17,18]

The standard PCNSL therapy is chemotherapy and radiotherapy. Chemotherapy can increase the patient's life expectancy, especially if combined with radiotherapy. High dose Methotrexate (high-dose methotrexate/HD-MTX) is commonly used for the treatment of PCNSL, where the provision of intrathecal MTX can carry high doses of systemic MTX (8 grams/m2). Drugs that suppress osmotic pressure can also be given to open the blood-brain barrier to facilitate the delivery of the drug to the lesion. Previous studies showed five cycles of HD-MTX (3.5 g/m2) and procarbazine (100mg/m2/day) had a good effect on patients, of which approximately 90% provide an objective response and the average life expectancy increased to 60 months.[23] A combination therapy involving several regimens such as HD-MTX, temozolomide, and rituximab is the therapy of choice for PCNSL.[24,25] Temozolomide is a chemotherapy agent with oral

bioavailability that can penetrate the blood-brain barrier and can be effective in patients with glioma, leukemia, lymphoma, and melanoma.[23] Every 1 gram/m2 dose of MTX has a tumoricidal effect as high as the brain parenchyma and 3 gram/m2 MTX dose has a tumoricidal effect as high as cerebrospinal fluid. Giving MTX requires intensive monitoring by calculating MTX serum levels.[27] Whole-brain radiation therapy is limited to dura tumors and is closely related to high neurotoxic risk in patients over 60 years old. However, the initial response of radiation therapy in immunocompetent patients is better than immunocompromised patients. The response to the duration of single radiation therapy is short, with an average life expectancy of only 18 months.[27] The main choice for PCNSL radiation therapy is 40-50 Gy whole-brain radiation followed by local radiation with 60 Gy in the region that has oedema.[26]

The surgical technique, as a PCNSL therapy option, is still being debated. Total tumor excision is not recommended because these tumors are generally located in deep locations so that the risk of postoperative complications will increase.[20,21] Surgical intervention is only used for stereotactic biopsy for diagnostic purposes.[20] However, some recent studies say that resection can be a PCNSL therapy option, especially if the surgery is combined with chemotherapy and radiotherapy regimens. Postoperative symptoms in some final studies show improvement without complications. Tumor resection is also recommended as the first-line therapy for patients with a single lesion and there has been an increase in intracranial pressure.[22]

PCNSL has a poor prognosis, and the patient's life expectancy ranges from 3-6 months without therapy, where single chemotherapy or combination with radiotherapy can increase life expectancy to 25-60 months.[8,9] Younger patients (under 60 years) have good immunity, and patients, where lymphoma does not involve meninges or ventricular proximal regions, have a better prognosis. Serum LDH concentration is also an independent prognostic marker, where elevated LDH and protein levels in the cerebrospinal cavity generally indicate a poor prognostic.

Conclusion

PCNSL is a rare type of non-Hodgkin's lymphoma that develops outside the lymph nodes (extranodal). The clinical manifestations of PCNSL are broad and non-specific, often misdiagnosed with metastatic tumors, gliomas, and cerebral toxoplasmosis. A physical evaluation and neurological examination, complete cognitive function evaluation, laboratory evaluation (determination of serum LDH, liver and kidney function, HIV serology), lumbar puncture for cerebrospinal fluid cytology, CT scan of the thorax/abdomen/pelvis, spinal cord biopsy, and ophthalmological examination with lamp-slits must be taken to diagnose PCSNL. Early diagnosis of PCNSL is very important and is needed to start appropriate and adequate therapy. HD-MTX is the PCNSL of choice therapy and will have a better prognosis if combined with radiotherapy. Generally, surgical excision is not recommended; surgery is used to carry out biopsies for diagnostic purposes only. Recent research supports that surgical resection may be the choice for the management of PCNSL, especially when surgical resection is combined with chemotherapy and radiotherapy regimens but is still debated.

Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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