A PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA PATIENT WITH DIABETES MELLITUS GETTING CHEMOTHERAPY AND CORTICOSTEROID

Ammar, Pradana Zaky Romadhon

ammar.unair@outlook.com, zaky.romadhon@fk.unair.ac.id

Division of Medical Oncology Hematology, Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Hospital, Surabaya, Indonesia

Abstract

Primary Central Nervous System Lymphoma (PCNSL) is a rare form of aggressive extranodal non-Hodgkin's lymphoma. Treatment modalities for PCNSL cases have developed in the last few decades, with no universally-agreed consensus regarding the optimal treatment regimen to date. We report a 61-year-old patient with right limb weakness, decreased consciousness, and a history of recurrent seizures. The patient had a MSCT examination on the head, with and without contrast, showing an enhancing solid mass with perifocal edema around it in the right frontal lobe. On immunohistochemical histopathological examination of cerebral material, the conclusion was Non-Hodgkin Lymphoma B cell type high grade. The patient was diagnosed with Non-Hodgkin Lymphoma Cerebral B cell type high grade. The patient was subjected to chemotherapy with HD-MTX (high-dose methotrexate) and rituximab therapy for 6 cycles, in combination with dexamethasone. Chemotherapy evaluation after 6 cycles showed a complete response to therapy without any drug side effects from chemotherapy with consciousness returning to normal and limb weakness gradually improving.

Keywords: Primary Central Nervous System Lymphoma, Non-Hodgkin Lymphoma, Chemotherapy

1. INTRODUCTION

Primary Central Nervous System Lymphoma (PCNSL) is an aggressive extranodal non-Hodgkin lymphoma, which is an aggressive type of cancer, confined to the craniospinal axis without any evidence of systemic involvement manifesting in the brain, eyes, leptomeninges, and spinal cord (Cai et al., 2019). More than 90% cases are histologically classified as diffuse large B-cell lymphoma (DLCBL) (Low et al., 2018). The incidence of PCNSL is about 0.47 per 100,000 population each year (Kurt et al, 2019). These cases accounted for about 2% of all brain tumor occurrences, about 4-6% of all extranodal lymphoma cases, and about 1% of all lymphoma cases (Cai et al., 2019). Those numbers have increased over the last three decades, and was reported to occur both in immunocompromised and immunocompetent patients. The median age at diagnosis in PCNSL cases was around 65 years. The most significant increase was experienced by older people around the age of 60 years (Mendez & Grommes, 2018).

PCNSL diagnosis is based on clinical manifestations obtained from the patient as well as supporting examinations such as CT-Scan and MRI which can be used to observe the presence and the location of lesions, as well as the gold standard diagnostic procedure requiring pathological examination through stereotactic biopsy. To date,

therapy modalities of this case is still in clinical trials, so there is still much debate concerning its management. There are several therapy modalities used today such as chemotherapy, radiotherapy, immunotherapy, and surgery. In addition, in patients with brain tumors and brain edema, it is recommended that low to moderate doses of dexamethasone be administered (Cai et al., 2019).

In the following, we report a case of a patient with non-Hodgkin's lymphoma of the primary central nervous system with diabetes mellitus, which is rarely encountered with a high-dose methotrexate treatment modality approach with corticosteroid administration.

2. CASE

A male patient aged 61 years, living in Lambangan village of Sidoarjo, was a referral patient from the Sidoarjo General Hospital to the Emergency Room of Dr. Soetomo Surabaya General Hospital. The patient complained of decreased consciousness and was admitted to the hospital through the Emergency Room on October 28, 2019.

From heteroanamnesis, it was revealed that the patient had experienced right limb weakness for the past 9 months. This condition was getting worse in the last 3 months. In the last 2 weeks, the patient had experienced decreased consciousness that was intermittent. History of seizures showed occurrences about 5 months ago. The patient was conscious both before and after the seizures. Seizures happened only 1 time in 1 day. During the last 5 months, seizures were experienced 4 times. The patient had been treated with diazepam for 2 months almost regularly and had never experienced a relapse until now. History of headaches had been felt since 6 months ago, was intermittent and was getting worse in the last 3 months. History of weight loss showed a decrease of 8 kg in 3 months. Complaints of decreased appetite were reported from the beginning of 2019 until now. Complaints of nausea were often experienced in the last 6 months, but involved no vomiting. Complaints of intermittent subfebrile were experienced in the last 3 months. However, the fever was getting worse in the last 1 month before being hospitalized. History of intermittent blurred visions were experienced the last 2 months.

The patient had MSCT Scan of the head with and without contrast on July 17, 2019. The result revealed an enhancing solid mass with perifocal edema around it in the right frontal lobe with a size of 4.58 cm x 2.97 cm which caused a midline shift of +/- 0.7 cm with subcentimer lymph nodes found in the right and left upper paratracheal (see Figure 1).

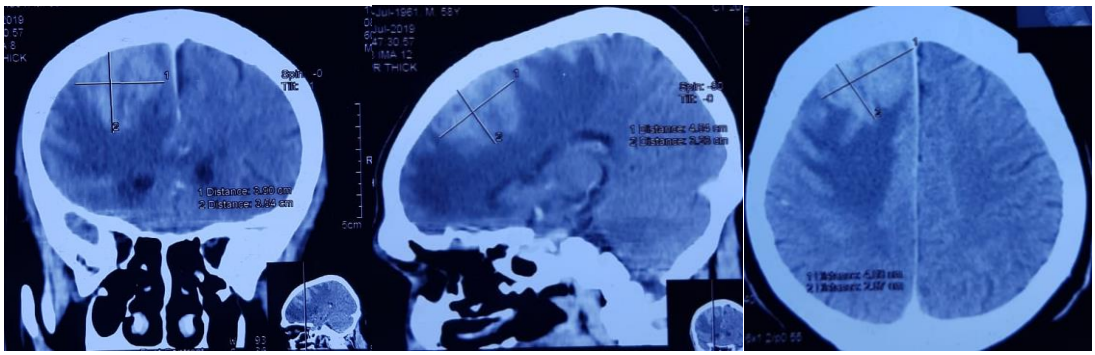

Figure 1. MSCT Scan of the head. enhancing solid mass with perifocal edema around it in the right frontal lobe with a size of 4.58 cm x 2.97 cm which caused a midline shift of +/- 0.7 cm with subcentimer lymph nodes found in the right and left upper paratracheal

The patient underwent surgery as well as tissue collection for biopsy on August 23, 2019. The patient underwent MSCT Scan of the head with and without contrast on September 28, 2019. The result showed an enhancing solid mass with perifocal edema around it in the right frontal lobe with a size of 5.82 cm x 6.53 cm which caused a midline shift of +/- 0.9 cm with a KGB size of +/- 0.9 cm in the right upper paratracheal and +/- 0.4 cm in the left upper paratracheal, a KGB size of +/- 0.5 cm in the right submandibular and +/- 0.4 cm in the left submandibular (see Figure 2).

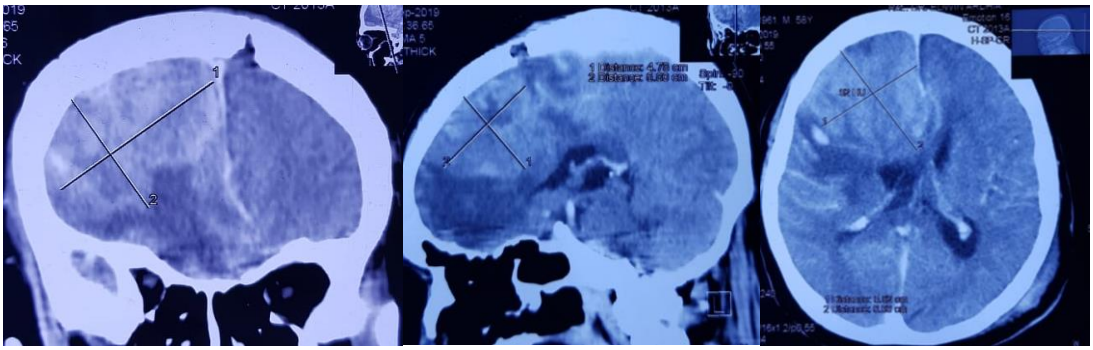

Figure 2. MSCT Scan of the head. enhancing solid mass with perifocal edema around it in the right frontal lobe with a size of 5.82 cm x 6.53 cm which caused a midline shift of +/- 0.9 cm with a KGB size of +/- 0.9 cm in the right upper paratracheal and +/- 0.4 cm in the left upper paratracheal, a KGB size of +/- 0.5 cm in the right submandibular and +/- 0.4 cm in the left submandibular

The results of ultrasound examination of the abdomen and lymph nodes did not show liver metastases and no lymphadenopathy was observed. On October 3, 2019, the results of histopathological immunohistochemical examination of cerebral material were obtained with the conclusion that Non-Hodgkin Lymphoma B cell type high grade CD 20 was positive, Ki 67 proliferation index 70% (see Figure 3). The patient underwent chest X-ray examination with no visible pulmonary manifestations of NHL and no prominent casts were observed.

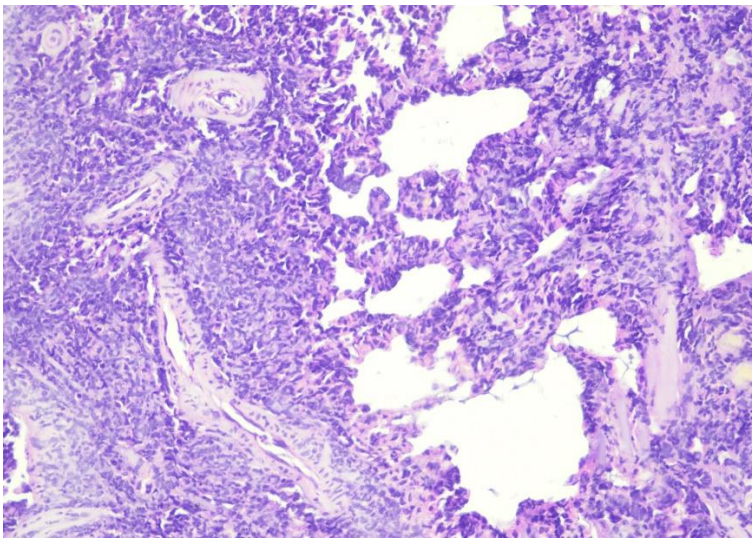

Figure 3. The histopathological immunohistochemical examination of cerebral material described Non-Hodgkin Lymphoma

On physical examination, general condition was weak and consciousness was somnolence with GCS 3-4-5. Motoric strength of upper and lower right extremities was on a scale of 2. Motoric strength of upper and lower left extremities was on a scale of 5. Examination of the olfactory I nerve was within normal limits. Meanwhile, examination of the optic nerve II oculi dextra 2/60 (bedsite) oculi sinistra 2/60 (bedsite).

Laboratory examination during hospitalized revealed hemoglobin at 10.5 g/dl, hematocrit at 32.3%, leukocytes at 10.440/uL, neutrophils at 69.2%, lymphocytes at 17.8%, basophils at 0.7%, eosinophils at 3.1%, monocytes at 9.2%, platelets at 363000/uL, MCV at 90.2 fL, MCH at 28.8 pg, MCHC at 33.4 g/dL, current glucose at 308, BUN at 11 mg/dL, serum creatinine at 0.84 mg/dL, SGOT at 38 U/L, SGPT at 48 U/L, Sodium at 135 mmol/L, Potassium at 4.5 mmol/L, Cl at 99 mmol/L, Albumin at 3.2 g/dL, LDH at 635 U/L, non-reactive HBsAg, non-reactive Anti HCV, and non-reactive HIV test.

Based on the heteroanamnesis, physical examination, and supporting examinations, the patient was diagnosed Non-Hodgkin Lymphoma B cell type high grade stadium II B CD 20 positive and unregulated type 2 diabetes mellitus. The patient was planned chemotherapy with a regimen of 3000 mg methotrexate, 500 mg rituximab given in 6 cycles every 21 days, and dexamethasone starting at a dose of 1x16 mg until the dose decreased by 1x1 mg. Patient getting insulin rapid acting actrapid 3 x 8 IU for blood sugar regulation.

At the 3rd post-chemotherapy, the patient showed an improvement in consciousness with compos mentis consciousness GCS 4-5-6, vital signs within normal limits, and a Karnofsky score of 70. Motor strength of the upper and lower right extremities was on a scale of 3, and the left extremities were on a scale of 5. The 3rd post-chemotherapy laboratory test was found to be almost within normal limits and the LDH level was 315 U/L.

At the 6th post-chemotherapy, the patient showed an improvement in consciousness with compos mentis GCS 4-5-6, vital signs within normal limits, and a Karnofsky score of 80. Motor strength of the upper and lower right extremities was in a scale of 4, while the left extremities were in a scale of 5. The patient had been advised for physiotherapy exercises with the medical rehabilitation department. The patient also received dexamethasone therapy starting at a dose of 16 mg at the beginning of chemotherapy and receiving gradually-decreased dose until 1 mg after chemotherapy. Laboratory examination results after the 6th chemotherapy were found to be within normal limits, blood sugar at 196, and LDH examination at 208 U/L. The patient was examined by MSCT of the head with and without contrast on March 14, 2020. The results revealed tentacle edema in the right frontotemporal and left frontal lobes without discrete mass and a calvaria defect in the right frontal region due to post-surgery (see Figure 4). The patient received dexamethasone therapy with a maintenance dose of 4 mg – 2 mg – 1 mg at Sidoarjo General Hospital for brain edema. After the 6th chemotherapy, the patient showed a complete response to therapy with drug side effects grade 0. The patient's daily activities after undergoing chemotherapy began to be active.

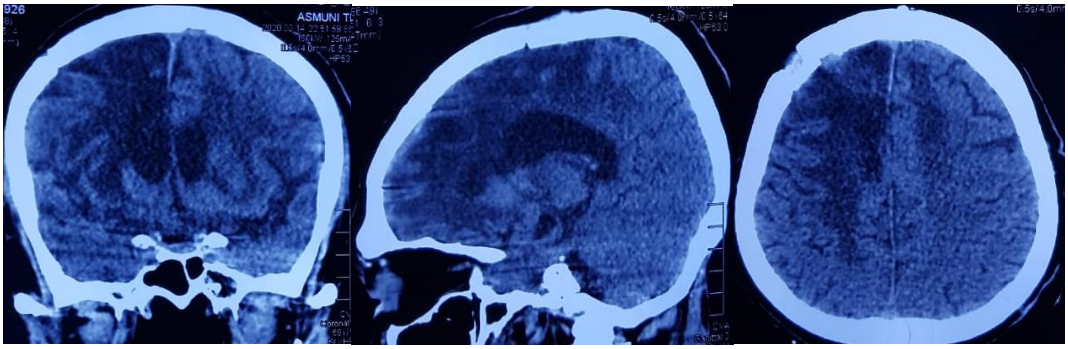

Figure 4. Discrete mass not visible with tentacle edema in the right frontotemporal and left frontal lobes

3. DISCUSSION

Primary Central Nervous System Lymphoma is a rare form of aggressive extranodal non-Hodgkin's lymphoma. This disease is an aggressive type of cancer, confined to the craniospinal axis without any evidence of systemic involvement manifesting in the brain, eyes, leptomeninges, and spinal cord (Cai et al., 2019). More than 90% cases were histologically classified as diffuse large B-cell lymphoma (DLCBL) (Low et al., 2018).

Based on Surveillance, Epidemiology, and End Results (SEER) data, the median age at diagnosis in PCNSL cases was around 65 years. The most significant increase in age was experienced by older people around the age of 60 years (Mendez & Grommes, 2018). The incidence of this case is about 0.47 per 100,000 population each year (Kurt et al, 2019). Incidence by gender was found to be more common in men than women with a ratio of 1.35:1 and there was no difference in incidence in certain races (Baumgarten et al., 2018).

PCNSL has been observed to occur mainly in immunocompromised individuals. In people with immunodeficient, there is a close relationship between the incidence of lymphoma and exposure to Epstein-Barr Virus (EBV) (Zhang et al., 2012; Kurt et al, 2019). In addition, factors that can raise the incidence of this lymphoma case include family medical history of the disease as well as exposures at work and environmental by pesticides and herbicides (George et al., 2018).

Clinical manifestations in PCNSL patients vary in its development of the nervous system such as symptoms of focal neurological deficits (56%-70%), changes in mental status, and changes in behavior (32%-43%). Symptoms of increased intracranial pressure can also occur such as headache, nausea, vomiting, papilledema (32%-33%), and seizures (11%-14%). This clinical presentation depends on the neuroanatomical location of the lymphoma (Grommes & Deangelis, 2017). In addition, patients may also experience visual disturbances such as blurred vision, decreased visual acuity, floaters, eye pain, and photophobia (4%). Some patients also have complaints of weight loss accompanied by decreased appetite (Mendez et al., 2018; Yang et al., 2018).

Procedures in establishing the PCNSL diagnosis can be evaluated in several ways, such as the use of Magnetic Resonance Imaging (MRI) of the head with gadolinium contrast to obtain optimal imaging of the brain parenchyma. However, the use of Computed Tomography (CT) Scan can also replace the function of MRI if it is medically contraindicated in patients who have a cardiac pacemaker installed or MRI is not available at the hospital. In addition, all patients should have a lumbar puncture performed for cerebrospinal fluid cytology unless medically contraindicated due to increased intracranial pressure. This interpretation of cerebrospinal fluid can help to observe

the cell count, beta-2 microglobulin, immunoglobulin H gene, and flow cytometry (Kurt et al, 2019). The gold standard examination in establishing this diagnosis is histopathological examination with stereotactic brain biopsy or with subtotal resection when considered safe (Cai et al., 2019).

To this date, the molecular and cellular pathogenesis underlying the occurrence of PCNSL is still hard to explain. The cellular and molecular mechanisms leading to neoplastic lymphocytic infiltration of the central nervous system can be observed in primary central nervous system lymphomas. There are 3 main things that are fundamental in understanding the nature of PCNSL, namely the histogenetic origin of tumor cells, the mechanism of transformation, and the role of the microenvironment in the central nervous system. The process of B cell differentiation can provide clues to understand the histogenetic origins in PCNSL. Mechanisms of point mutation, addition of genetic material, loss of genetic material, and DNA hypermethylation contribute to the pathogenesis of PCNSL (Cai et al., 2019; Kurt et al, 2019).

Treatment modalities in PCNSL cases have developed in the last few decades, but there is no universally-agreed consensus regarding the optimal treatment regimen. Experts currently agree that high-dose methotrexate is still the mainstay of therapy and there are many other retrospective and prospective studies using single or combination chemotherapy regimens, including radiotherapy and surgery in treating these cases (Cai et al., 2019). The role of surgery in PCNSL is generally limited to stereotactic biopsies due to the widely infiltrative and diffuse nature of tumor growth. This surgical resection may increase the risk of permanent neurologic deficits in diseases that often involve deeper structures. (Grommes & DeAngelis, 2017; Niparuck et al., 2019).

Chemotherapy treatment in monotherapy manner with high doses of methotrexate has played an important role in treating PCNSL (Laghari et al., 2018). Methotrexate is a folate antagonist that interferes with DNA synthesis by reaching therapeutic concentrations in the central nervous system. This methotrexate can penetrate the blood brain barrier with high doses of more than 1.5 g/m^2, rapidly and intravenously administered in about 3-4 hours (Grommes & DeAngelis, 2017). However, there are no clinical trials that have clearly shown an advantage in using doses greater than 3 g/m^2. The clinical application of methotrexate at doses greater than 3 g/m^2 is often met with side effects such as renal impairment, bone marrow toxicity, pneumonitis, and mucositis. In such case, a dose reduction during therapy is needed. Although high-dose methotrexate as a single agent is quite effective in induction therapy, clinical studies have shown an initial recurrence rate of 13.7 months. Such therapy should be at least in 6 cycles and in conjunction with adequate supportive care with hydration, urine alkalinization, administration of leucovorin, and monitoring of methotrexate levels. Monotherapy with high-dose methotrexate achieves complete remission in approximately 40% of patients and is relatively well tolerated and with a low incidence of toxicity. High doses of methotrexate are usually given with folic acid (leucovorin) to increase 5-fluoruracil with a mechanism to neutralize the toxicity of the folic acid antagonist (methotrexate) such as reducing the side effects of myelotoxicity, hepatotoxicity, and various neurological symptoms. In elderly patients of over 60 years, the dose of methotrexate may require an adjustment due to decreased creatinine clearance. The minimum safe creatinine clearance limit for starting treatment is usually above 50 ml/minute (Siegal & Bairey, 2019). If the patient has a sub-optimal initial creatinine clearance but still above 50 ml/min, a 50% dose reduction from the standard methotrexate regimen of 1-8 g/m2 is needed to reduce the effect of nephrotoxicity (Ferreri et al., 2019).

Administration of corticosteroids is aimed to reduce brain edema in brain tumor patients through various mechanisms, namely inhibition of phospholipase A2 (arachidonic acid enzyme), stabilization of lysosomal membranes, and improvement of peritumor microcirculation. Currently, dexamethasone is the most widely used corticosteroid to reduce brain edema in patients with tumor. Dexamethasone is six times more potent than prednisone. Administration of high-dose 16 mg dexamethasone is recommended in the treatment of brain edema in brain tumor patients with a gradually-decreased dose every week. However, high doses of 16 mg in some studies have higher toxicity than low (4 mg/day) or moderate (8 mg/day) doses, such as muscle weakness, hyperglycemia, fluid retention, visual disturbances, tremors, psychological changes, and brain atrophy (Dietrich et al., 2011).

Corticosteroids reduce the effect of glycemic control as they increase peripheral insulin resistance and suppress insulin production. Administration of dexaamethasone more than 8 mg/day has a high hyperglycemic effect and requires insulin dose adjustment in brain tumor patients who suffer from diabetes mellitus (Gosmanov et al., 2013 & Kostaras et al., 2014). Daily doses of steroids such as IV hydrocortisone or oral dexamethasone can cause hyperglycemia throughout the day for 24 hours. Close guidance of insulin therapy in patients with diabetes mellitus using steroids can be given subcutaneous insulin basal-bolus regimen with basal insulin and or with prandial insulin which is the most suitable option to achieve blood glucose target. Insulin dose adjustments are made for blood glucose control if the steroid dose is increased or decreased. (Perkeni, 2019 & Perez et al., 2015).

Several clinical trials have shown that the combination of high-dose methotrexate with other cytostatic agents is still feasible in older patients with various median overall survival rates, ORR (overall response rate), CR (complete response), and PFS (progression-free survival). Some of the combinations include cytarabine, temozolomide, procarbazine, vincristine, ifosfamide, and thiotepa (Kasenda et al., 2015). The combination regimens currently used are R-MT, R-MPV, and MATRIx (Cai et al., 2019).

As for prognosis to predict outcomes and better stratification of patients in clinical trials, 3 scoring systems can be used, including the International Extranodal Lymphoma Study Group (IELSG) score, Memorial Sloan Kettering Cancer Center (MSKCC) prognostic score, and Nottingham/Barcelona (NB) score. The IELSG scoring uses 5 parameters, namely age, ECOG performance score, LDH levels, protein concentration in CSF, and inner brain involvement. A score of 0-1 has a low risk, 2-3 has a moderate risk, and 4-5 has a high risk which correlates with a 2-year survival rate of 80%, 48%, or 15%. Meanwhile, the MSKCC scoring is categorized into 3 groups based on Karnofsky's age and performance status as follows: the first group with age of 50 years, the second group with age ≥ 50 years and Karnofsky performance status 70, and the third group with age of 50 years and Karnofsky performance status 70. These three groups are respectively associated with median overall survival of 8.5 years, 3.2 years, and 1.1 years. Meanwhile, the NB scoring uses 3 parameters, namely age, performance status, and multifocal or unifocal disease expansion (Grommes & DeAngelis, 2017).

4. CONCLUSION

It has been reported that a 61-year-old male patient was diagnosed Non-Hodgkin Lymphoma B cell type high grade stadium II B CD 20 positive and unregulated type 2 diabetes mellitus The patient had been subjected to MSCT of the head and immunohistochemical histopathological examination of the brain. The patient had undergone chemotherapy with HD-MTX (high-dose methotrexate) therapy at a dose of 3000 mg and rituximab at a dose of 500

mg for 6 cycles every 21 days, as well as dexamethasone from high to low doses. Patient getting insulin rapid acting actrapid 3 x 8 IU for blood sugar regulation. Evaluation of the patient's condition after 6 cycles of chemotherapy showed a complete response to therapy without any drug side effects from chemotherapy. The patient has experienced an improvement in full consciousness with limbs gradually returning to normal.

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