One Health Journal of Nepal

Case Report Open Access

Primary CNS Lymphoma: A Case Series

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ABSTRACT:

Primary CNS Lymphoma is a very rare and unique form of Lymphoma confined in the brain, eyes, leptomeninges or spinal cord without any Systemic involvement. It occurs both in immunocompromised and immunocompetent individuals. It offers a unique challenge in diagnosis and treatment as prior use of steroids can misguide diagnosis and blood brain barrier limiting the use of standard CHOP regimen. Here, we report six cases of PCNSL in Nepal that present the clinical pathologic profile, treatment strategies and outcomes. Patients were treated with multimodality treatment approach including chemotherapy,monoclonal antibodies and radiotherapy. Patients were followed up on for at least a year after treatment and were in good health, with some complaining of gait disturbances and forgetfulness that were affecting their quality of life. These issues were milder or not seenin younger fit patients. patients.

Keywords: *Case report; Lymphoma; Primary central nervous system.*

INTRODUCTION

Primary Central Nervous System Lymphoma (PCNSL) is a very rare and unique form of Lymphoma. It is confined in the brain, eyes, leptomeninges or spinal cord with absence of any Systemic involvement and occurs in an immune privileged or sanctuary site, the CNS system. It accounts for 2%of CNS tumors and 5-8% of extra nodal lymphomas involving the brain exclusively.[1] Primary CNS Lymphoma is historically an AIDS defining tumor with HIV infected people being at least 1000 times more at risk of suffering from PCNSL. However, with the advent of effective HAART the incidence of PCNSL incidence is gradually decreasing in immunocompromised patients. Its incidence however hasn't changed much in immunocompetent old patients. Some other risk factors associated with PCNSL are organ transplant recipients receiving immunosuppressive drugs, prior Malignancies, autoimmune and immunomodulating disease.[2] Our case series of PCNSL in a tertiary cancer center in Nepal reported the clinical pathologic profile, treatment strategies and outcomes in a limited number of cases occurring at Nepal Cancer Hospital and Research Center from 2015. A total of 6 cases are being presented which were treated at Nepal Cancer Hospital and Research Center for PCNSL.

CASE SERIES

Case 1:

A 35-year-old male migrant worker was evaluated for progressive loss of vision of the left eye over the last 1-2 years. Following near complete vision loss over the left eye with no light perception, disorientation and vomiting he was evaluated at a center abroad. Following preliminary investigation he was referred back to Nepal. A CECT head done on 2015/5/28 showed multiple edematous lesions in the left temporal, cerebellum and brainstem. USG Abdomen was normal. MRI Brain done was suggestive of Primary CNS Lymphoma following which he underwent Stereotactic Biopsy (2015/06). A grayish appearing multiple mass lesion was sent from sampling which was morphologically consistent for diffuse large cell lymphoma. Other pertinent lab

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reports show normal Complete Blood Count, Renal and Liver function. HIV, Hepatitis B and C tests were non-reactive. CSF examination showed high WBC count with increased protein levels. Ophthalmic evaluation showed papilledema on right side with atrophic disc on left side with absent pupillary reaction on left side. He was referred to our center for further management. A thorough metastatic workup revealed no evidence of disease elsewhere, BMA-Normal, USG Tests- Normal. A High Dose Methotrexate and Cytarabine consolidation-based chemotherapy was planned for the patient. He underwent 5 cycles of high dose Methotrexate followed by 2 cycles of Cytarabine Consolidation. End of treatment evaluation with CECT head showed meningoencephalitis changes with no evidence of any residual disease. He followed up at our center till Dec 2016 at that point of time he had good performance status he however was lost to follow up thereafter.

Case 2:

50 years/Male was evaluated for dizziness, difficulty in head holding and vomiting 1 year prior to presentation at our center. He had MRI whole spine done on 2017/5 which showed intensely enhancing nodular lesion in left cerebellum with differentials of solid Hemangioblastoma metastasis. 1 year later a repeat MRI scan showed intensely enhancing mass in the brainstem with mild hydrocephalus with features suggestive of glioma pilocytic astrocytoma. A lumbar puncture was negative for malignancy. He underwent suboccipital craniotomy with excision of lesion on 2018/4. Post-operative histopathological reports showed High Grade NHL with IHC analysis showing positivity of CD 20, CD3 BCL-6 MUM1 and BCL-2 and C-Myc, CD 99 /CFAFP/CD 10 was negative. DeAngelis protocol was started for the patient Anti CD 20 monoclonal antibody (Rituximab) couldn't be given due to financial constraints. Post 5 cycles of chemotherapy patients had partial response to therapy with enhancing patchy area in right side of midbrain with nodular enhancement in pons with heterogeneous enhancing right caudate head. He was referred to radiation therapy and underwent 3 6Gy 20 Whole Brain Radiation Therapy (WBRT) followed by MRT boost of 9Gy in 5 to residual lesions. Patient complained of slurred speech and gait disturbance prior to initiation of therapy which continued until radiation. He was lost to follow up post radiotherapy.

Case 3:

59 years/Male was evaluated for weakness of the right side of body, headache,nausea and vomiting with short term memory loss of 4months (2018/4). He had past medical history of PTB 20yrs back (ATT completed) CECT head done on 2018/04 showed homogeneously enhancing hyperdense corpus callosal mass extending to the adjacent deep white matters of fronto-parietal lobes with perilesional edema. MRI Brain showed corpus callosal mass with extension and perilesional edema in adjacent white matters of fronto-parietal lobes (35x38x26) mm. MRS showed increased choline and creatine with decreased NAA. He was administered 3 doses of Dexona due to worsening symptoms. He had marked improvement in symptoms, no further intervention could be carried out and repeated. MRI Brain was done 2 weeks later which showed an ill-defined enhancing mass in splenium and body corpus callosum extending into the septum pellucidum with gross perilesional edema (3.9x3.9x3.0). A repeat biopsy was tried but failed. With these work ups and drug history he came to our center for further management. MRI Brain on13/07/2018 Multiple small sized lesions in left hippocampal region medial to temporal horn of left lateral ventricle, largest measuring 9x10mm. Lab reports showed normal CBC, RFT and LFT. CSF examination grossly normal HIV, HBV, and HCV: Non-reactive. Ophthalmologic examination revealed circumscribed choroidal hemangioma, Foveal pigment changes. Brain biopsy was not possible due to deep seated lesion and prior administration of steroids. CECT Chest/Abdomen and USG Scrotum reported no significant findings. After thorough discussion on the nature of disease and high clinical and radiologic suspicion of Primary CNS lymphoma patient was started on De-angelis protocol. Following induction chemotherapy MRI Head showed 7x4mm and 5x4mm size residual lesion in the left temporal lobe. He also needed anticoagulant therapy for DVT of right lower limb. RT started from 12/12/2018-14/01/2019. Post treatment follow up recently is "CR". Consolidation therapy was not given as the patient defaulted.

Case 4:

77 years/Female, hypertensive, diabetic patient evaluated for disorientation and forgetfulness since 1 month, associated with generalized weakness and anorexia. MRI brain on 12/02/2019: Mass involving the splenium of corpus callosum crossing the midline showing homogenous enhancement and diffusion restriction and similar enhancing lesion in left medial temporal lobe (1.3x1 cm) PET CT whole body on 20/02/2019: FDG avid (SUVmax: 13.7)(45x20x20mm) homogeneously enhancing lesion in the region of splenium of corpus callosum extending into both cerebral hemispheres. No metabolically active disease elsewhere. Biopsy from occipital lobe and splenium on 05/03/2019: suggestive of NHL. IHC on 2019/03/12: Occipital lobe, splenium: DLBCL, activated B cell phenotype. CD20 positive, Bcl2: Positive, PAX5: positive, MUM1 few cells positive, Ki67%:80%. HIV, HBsAg and anti HCV non-reactive. CSF study revealed slightly raised protein levels. Referred to our center for further management. Tumor Board discussion was done as the patient wouldn't tolerate polychemotherapy induction therapy. It was decided to offer a patient palliative nature of treatment including Rituximab and Temozolomide based therapy however the legal guardian refused chemotherapy and opted for

Local Radiotherapy She was planned and received 25 of WBRT. Post-treatment MRI brain on 01/07/2019: No evidence of enhancing focal lesion in the brain. Impression Complete Remission.

Case 5:

69 years/Male, hypertensive, nondiabetic patient evaluated for gradual progression of right sided weakness, slurring of speech and confusion for 1 month. MRI brain on 14/08/2018: Multiple enhancing left frontal SOL with Edema. CT chest and abdomen on (14/09/2019). Mild B/L pleural thickening. Tiny non enhancing endobronchial lesion (3mm) in right main bronchus and Normal abdomen and pelvic scan. Underwent left frontal craniotomy and excision on 22/08/2018: at another center. HPE: Small round cell tumor consistent with lymphoma of CNS. IHC: DLBCL-non germinal center b-cell type. He was thereafter referred to our center for further management.

USG scrotum: B/L multiple testicular microlithiasis,epididymal cysts right, minimal hydrocele B/L, ill-defined hypoechoic area in inferomedial aspect of right testis. Testicular lesions were kept on observation. MRI whole spine on 17/09/2018: mild disc bulge at C5-C6 and C6-C7 level and degenerative changes in L5. And MRI brain on 17/09/2018:Ill-defined hypo-intense area in left frontal lobe with mild hyper intensities and peripheral enhancement. Enhancing lesion in left frontal lobe in parasagittal location, bone marrow examination on 17/09/2018: Reactive normocellular marrow with erythroid hyperplasia showing no marrow involvement by atypical lymphoid cells. Ophthalmic examination: B/L hyperopia and presbyopia. Planned and started on De-Angelis protocol from 18/09/2018. Post chemo evaluation with MRI: Post op changes with encephalomalacia involving the left frontal lobe with surrounding reactive gliosis. Resolution of previously enhancing lesion in left frontal lobe. Planned for WBRT and started from 2018/12/24. He suffered from severe skin rashes suspicious of measles. He needed critical care management and treatment. Radiotherapy was kept on hold due to poor G.C and restarted after a delay of 10days. Post treatment evaluation showed "CR" however he has persistent gait imbalance and complaints of forgetfulness.

Case 6:

24 years/Male, evaluated at center abroad for complaint of mass on right temporal region. CECT Head done on 04/08/2018 reported large intensely enhancing extra-axial mass along right fronto-parieto-temporal region seen, eroding adjacent bony calvarium. No abnormal enhancing lesion seen in adjacent cerebral parenchyma. Excision biopsy of tumor done on 12/10/2018 abroad. HPE and IHC revealed DLBCL, (LCA, CD20, bcl6: positive). He then returned back to Nepal after a month for further management. Pre evaluation with CECT head, neck, chest and abdomen done on 14/11/2018: post-operative changes with minimal extradural collection and no other significant findings. HIV, HbSAg, anti-HCV non-reactive. He was then planned and started on chemotherapy regimen based on De-Angelis protocol from 30/11/2018. Post 3 cycles chemo evaluation with MRI brain revealed no evidence of residual/recurrent lesion. Following 3 cycles of chemotherapy the patient had persistent and prolonged fever with chronic UTI and a considerable amount of weight loss ATT was started empirical but despite two weeks of treatment the patient's fever didn't subside. He was referred to our center in dismal circumstances. He needed extensive care with antibiotics and improved nutrition and gradually improved. He was able to continue treatment and was given the remaining course of Induction chemo followed by HiDAC consolidation at our center. Post treatment evaluation showed complete remission with hypereosinophilia at 2yrs follow up.

DISCUSSION

The diagnosis and treatment of PCNSL offers a unique challenge to practicing physicians, Patients usually present with significant CNS symptoms and on presentation patients usually have a high suspicion of more commonly occurring CNS tumors. In our case series a variety of CNS symptoms were observed with weakness of the limbs, forgetfulness and nausea and vomiting. MRI scan of the brain suggests multifocal lesions involving the parenchymal area of the supratentorial region with most common differential diagnosis of Glioma followed by metastatic disease and tuberculosis. Lymphoma cells are extremely sensitive to corticosteroid induced apoptosis It has been shown that prior corticosteroid administration decreased diagnostic yield in PCNSL by upto50%.[3]

The blood brain barrier limits the use of standard CHOP regimen in PCNSL due to poor drug penetration. Standard treatment includes an induction phase and a consolidation phase. Despite the rarity of cases some clinical trials have been conducted to establish the best induction strategies followed by consolidation modality and the treatment of PCNSL has evolved from WBRT as the standard of therapy to High Dose Methotrexate and Polychemotherapy including HDMTX and Rituximab as induction therapy to consolidation strategies designed to limit the use of RT or encourage low dose RT to limit neurotoxicity.[4] Ferreri et al. established Polychemotherapy(HDMTX+HiDAC) superior to HDMTX alone in <75 yrs. old patients. HDMTX+ HiDAC in induction chemotherapy compared to exclusive HDMTX, followed by RT improved ORR from 40-69%. PFS was prolonged from 3 months to 18months and OS at 3yrs 46% in HDMTX/HiDAC group.[5] This trial was followed by another study patients were divided into three groups receiving either HDMTX+HiDAC(Group1),

Rituximab+Group1 (Group2); or Thiotepa + Group2(R-MATRIX) Group followed by randomisation for either WBRT or ASCT Consolidation. They concluded R-MATRIX is a new standard of induction therapy. Trials designed to limit the use of RT or introduce low dose RT or omit it altogether during consolidation is being explored.[6] Morris et al. in their paper R-MVP followed by consolidation reduced dose WBRT and Cytarabine concluded PFS at 2 yrs. 77%, 3 yrs. OS at 87%and minimal neurotoxicity. However neurological complication will continuously remain low with long term follow-up remains to be answered.

More recently in strategies designed not to use RT altogether showed effective strategies omitting RT with MTR induction followed by EA consolidation conducted by Wielduwlit ML, Valles F Issa et al.[7] showed no difference but without evidence of neurotoxicity.

More often, an estimated 60% of Primary CNS lymphomas patients eventually relapse. A large portion of these patients are old and unable to tolerate HDT and ASCT. Treating strategies in relapsed setting includes rechallenging R-HDMTX therapy, to irradiating unirradiated patients, to exploring an array of targeted and novel agents in their newer role in treatment of PCNSL. Temsirolimus has shown short lived activity in Relapsed PCNSL.[8] Temozolomide is an alkylating agent that readily crosses the blood brain barrier, it is widely used in other CNS Tumors, when used in heavily pretreated relapsed PCNSL it induced a CR rate of 29%.[9] Temozolamide used together with MTX and Rituximab is also an effective induction therapy with significantly less side effects. Role of Ibrutinib , a first generation BTK inhibitors is promising, it has also shown an overall response rate of 83% but with higher incidences of aspergillosis,Cytopenias and mortality.[10] Single agent lenalidomide or in combination with Rituximab have shown an overall response rate of 63% in R/R PCNSL.[11] More recently Adoptive and immune checkpoint inhibitor immunotherapy has transformed treatment in malignant lymphomas, PCNSL expresses PDL-1 receptors, Role of Nivolumab and Pembrozilumab is being explored in clinical trials setting in R/R PCNSL. Nivolumab in a small case series showed excellent and prolonged response rates and their role in the treatment of R/R PCNSL looks promising.[12]

CONCLUSIONS

Our report elaborates 6 histopathologically diagnosed cases of Primary CNS Lymphoma. Patients with age ranging from 24-77 were evaluated at different centers all across the country and abroad for significant CNS symptoms. Except for one patient, almost all the other patients underwent DeAngelis-like of De Angellis protocol at our center with good tolerance and response to therapy. The exception was a 77 year old patient who was deemed unfit to undergo De Angelis protocol, she was strongly recommended by the medical team to receive Rituximab and Temolozomide based chemotherapy which was denied by her legal guardian following she underwent WBRT. Patients regularly followed up for at least 1 year post treatment and were in good state of health with some complaining of gait disturbance, forgetfulness affecting their quality of life,these problems were milder and not observed in younger fit patients however neurotoxicity post treatment is a major challenge PCNSL.

ACKNOWLEDGMENT

We would like to acknowledge the patients for giving consent to publish this case report.

CONSENT

Case Report Consent Form was signed by the patient.

CONFLICT OF INTEREST

None

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