Pediatric Primary Central Nervous System Lymphoma

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ABSTRACT

Introduction: Primary central nervous system lymphoma (PCNSL) is rare brain tumour in pediatric age group. Primary central nervous system lymphoma is an extra-nodal malignant tumour and is confined to brain, eyes, or leptomeninges.

Case report: We report the case of PCNSL in a nine year old child who presented to M.M. Hospital with the history of fever since 20 days (on and off), swelling over face and eyes for 16 days, deviation of mouth for 16 days, headache and vomiting for 3 to 4 days and loss of appetite for 3 days. Magnetic resonance imaging of the brain revealed a large poorly defined soft tissue enhancing mass involving skull base centered in basisphenoid with small parenchymal lesion in left frontal region.

Conclusion: Patient was managed with systemic chemotherapy in combination with radiotherapy. Intrathecal therapy reserved for cases with lymphomatous meningitis, and the role of ultra high dose therapy and stem cell rescue remain to be evaluated.

Keywords: Pediatric Primary Central Nervous System, Lymphoma

INTRODUCTION

It can affect all age groups, with a median age in the sixth decade in patients without AIDS.[1] Among AIDS patients, mean age of the disease presentation is younger (31 to 35 years). Primary central nervous system lymphoma has been diagnosed in HIV-positive children as young as 2 years. Affected B cells, proliferate without the controlling effect of the immune system and tend to form tumors. The clinical features of PCNSL at presentation reflect the neuroanatomic location of the lesions. The condition presents in four distinct anatomic distributions:

1. Solitary or diffuse intracranial mass lesions.
2. Leptomeningeal lesions.
3. Ocular lymphoma with or without other lesions.
4. Rare spinal cord lesions.

As far as neuroimaging evaluation is concerned, in a retrospective series of immunocompetent patients with PCNSL, the patients presented with a single brain lesion, either supratentorial, or involving frontoparietal lobes. Immunocompetent patients presented with focal neurologic deficits (50%), and behavioral changes (30%), clinical features of raised intracranial pressure [headaches, vomiting, and papilledema (25%)], and seizures (10%). Multiple lesions are seen in 30% to 40% of the cases. Diffuse periventricular involvement in PCNSL should be differentiated from multiple sclerosis. For immunocompromised patients, multiple ring-enhanced lesions on MRI should be differentiated from toxoplasmosis cerebri. On MRI, most lesions are hypointense on T1- weighted images, isotense or hyperintense on T2-weighted images. The majority of children with PCNSL, however, can achieve long-term remissions with intensive chemotherapy alone and cranial irradiation may be reserved for relapse cases.

CASE REPORT

A 9-year-old boy reported to paediatric department of M.M. Hospital, Mullana with the complaints of fever for 20 days (on and off), swelling over face and eyes for 16 days, deviation of mouth for 16 days, headache and vomiting for 3 to 4 days and loss of appetite for 3 days. Patient was born to parents of non-consanguineous marriage and low socioeconomic class. He was born after an uneventful pregnancy and delivery. The patient's weight, height, and head circumference were 19 kilograms (< 5thpercentile), 118 centimeters (<5th percentile), and 50 centimeters (~ 5th percentile) respectively.

On examination vitals were; BP –100/60mmHg, PR –80/min, RR – 22/min, Temp –98.6 F; On Central nervous system examination child was conscious, oriented to time, place and person. On cranial nerve examination there was right sided obliteration of nasolabial furrow, deviation of angle of mouth to the left side [Figure-1], inability to close the right eye tightly [Figure-2], absence of wrinkles on the forehead on the right side, unable to blow air on right side; which was suggestive of right sided facial nerve palsy. Rinne's test – bilateral bone conduction was better than air conduction (bilateral conductive deafness); gag reflex was absent which was suggestive of glossopharyngeal nerve palsy; sensation at palate was absent, uvula was deviated towards left side which was suggestive of right sided vagus nerve palsy; the tongue deviates towards the right side on protrusion [Figure-3] suggesting left sided hypoglossal nerve palsy. Motor and sensory examination was within normal limits. Cardiovascular, respiratory and gastrointestinal systems were within normal limits.

In laboratory tests, complete blood count, sodium, potassium, blood sugar, calcium, blood urea, nitrogen, creatinine, liver function tests, albumin, electrolytes, antiendomysial antibody (IgA), andgliadin antibody (IgG) was normal. The

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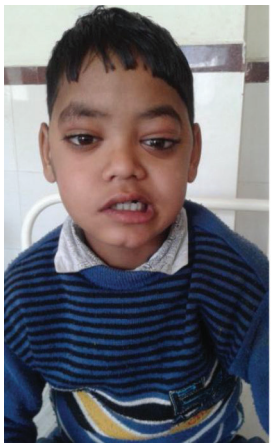
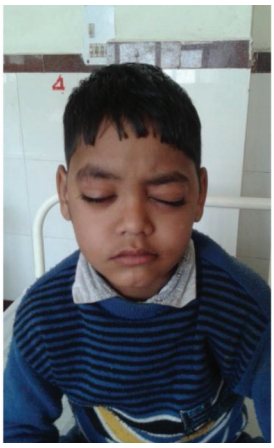

Figure-1: Drooping of angle of mouth with visible bilateral exopthalmos; **Figure-2:** Ptosis

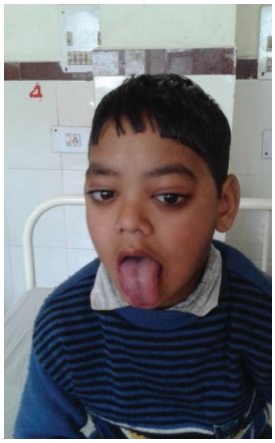

Figure-3: Deviation of Protruded Tongue

erythrocyte sedimentation rate was raised and C-reactive protein was 1 mg/dl. In flow-cytometry, CD4 was 8% and CD4/CD8 was 0.14. HIV test was negative. Concerning risk of herniation, lumbar puncture was not performed. Brain MRI revealed large poorly defined soft tissue enhancing mass involving skull base centered in basisphenoid with extensions including intradiploic extension and into nasopharynx, small parenchymal lesion in left frontal region with perilesional edema.

DISCUSSION

PRIMARY central nervous system lymphoma is an extra nodal malignant lesion confined to the brain, eyes, and leptomeninges. PCNSL cases represent 5% of primary brain tumors, and its incidence has been increasing in the last three decades. The
incidence is higher in AIDS patients. It can affect all age groups, with a median age in the sixth decade in patients without AIDS.[2] This tumor is rare in childhood. The common presenting clinical features were suggestive of increased intracranial pressure, such as headaches, vomiting, followed by cerebellar symptoms such as ataxia, and dysmetria. Seizures and hemiparesis were common. Other associated features were blurring of vision, diplopia, and proptosis. In pediatric cases metastases to brain and meninges from systemic malignancies are rare. Exceptions to this rule are pediatric leukemia and lymphoma involving brain. Classic findings of a space occupying lesion, including mass effect and surrounding vasogenic edema are seen on imaging studies of primary brain lymphoma in majority of patients. The patients with PCNSL might have several masses in the brain (supratentorial / infratentorial).

Radioimaging Features

Childhood PCNSL present as solitary mass or multifocal tumour. Most frequent tumor locations are parietal and frontal lobes, cerebellum, pituitary stalk, and hypothalamus.[3]

Cytological Features

Diagnosis is usually made by stereotactic biopsy, leptomeningeal biopsy, open biopsy, autopsy, or by immunocytochemical, cytogenetic, and polymerase chain reaction analysis of CSF. The DLBCL is the most common subtype. The most common immunophenotype was mature B-cell, followed by T-cell.

Prognosis

In paediatric patients with PCNSL, however, the prognosis has improved over the last 10 years. A review by Kai, et al., of paediatric treated cases found a the mean survival time of 03–70months, with majority of cases treated with cranial radiotherapy alone or combined with chemotherapy. A correlation between histological findings and prognosis can be inferred, with the histiocytic subtype being the most aggressive among published paediatric cases of PCNSL; the overall survival was only 3 to 4 months.[4] Lymphoblastic lymphoma, occuring frequently in children, have a worse prognosis with a relapse rate and leukemic transformation

Treatment

Long-term survival with chemotherapy alone without cranial radiotherapy had been observed.[5] Other possibilities for therapy include surgery, cranial radiotherapy alone, chemotherapy followed by cranial radiotherapy. Cranial radiotherapy prior to chemotherapy significantly increases neurotoxicity, and therefore it is not recommended.

Surgery Alone[6]

The utility of surgery in both paediatric and adult patients with PCNSL is limited to biopsy sampling.

Cranial Radiotherapy Alone

Nelson,et al.,[7] studied that 60% of patients suffered a relapse of the tumor with radiotherapy alone. In children there are concerns about high risk of secondary brain tumors along with risk of neurocognitive dysfunction. Treatment of paediatric PCNSLs with cranial radiotherapy alone is therefore not indicated, except in the palliative setting.

Chemotherapy Followed by Cranial Radiotherapy

Combination high-dose MTX and cranial radiotherapy results in better outcomes.[8] Chemotherapy regimens were MTX and AraC combined with dexamethasone or prednisone. Radiotherapy consisted of either cranial or craniospinal radiotherapy (12 to 50 Gy).

Chemotherapy Alone

Numerous studies in adults suggests that when drugs that

cross the BBB are used, patient survival is equivalent to that seen after combined therapy, with significantly fewer cognitive defects. International FAB LMB-96 study results in pediatric cases with CNS-positive B-cell non-Hodgkin lymphoma, in whom the abandonment of cranial irradiation and an additional course of systemic high-dose MTX and intrathecal chemotherapy resulted in better outcome. MTX is most important drug for the treatment of PCNSL.[9] MTX has a lymphoblastolytic action and ability to penetrate the CNS at doses of 1 g/m2 or more. Cytarabine also has a proven efficacy in PCNSL, especially at doses of 3 g/m2 or more. AraC in combination with MTX has better survival rates compared to MTX alone

Stem Cell Transplant

Autologous stem cell transplant in management of PCNSL, had shown survivals rates ranging from 51% to 70% at 5 years. Role of stem cell transplant as first-line treatment in pediatric PCNSL is controversial due to high incidence of neurotoxicity, specially in those patients who have previously received radiation therapy.[10]

CONCLUSION

The literature on pediatric PCNSL is sporadic due to the rarity of this disease. Headache and seizure may be the symptoms of a serious disease. The pediatric PCNSL cases might have several supratentorial and /or infratentorial) masses in the brain. The best management options are difficult in the absence of prospective studies. Based on our scrutiny of existing literature we suggest that the majority of pediatric patients can be cured with recommended dose multidrug chemotherapy and irradiation of brain reserved for refractory cases.

ABBREVIATIONS

ALCL = anaplastic large cell lymphoma; AraC = cytarabine; CHOP= cyclophosphamide, doxorubicin, and prednisolone; CNS = central nervous system; CSF = cerebrospinal fluid; DLBCL = diffuse large B-cell lymphoma; EBV = Epstein–Bar virus; MTX = methotrexate;

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