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Case Report

Intracranial disease in pediatric Hodgkin lymphoma-case report and review of literature

Nidhi Dhariwal[1,2], Nirmalya Roy Moulik[1,2], Vasudeva Bhat[2,3], Vasundhara Smriti[2,4], Sangeeta Kakoti[2,5], Sayak Choudhury[2,6], Epari Sridhar[2,7], Sumeet Gujral[2,7], Chetan Dhamne[1,2], Sneha Shah[2,6], Gaurav Narula[1,2], Shripad Banavali[1,2]

[1]Division of Pediatric Oncology, Department of Medical Oncology, Tata Memorial Hospital, Mumbai 400012, Maharashtra, India; [2]Homi Bhabha National Institute, Anushakti Nagar, Mumbai 400094, Maharashtra, India; [3]Department of Pediatric Hematology and Oncology, Manipal Academy of Higher Education, Manipal 576104, Karnataka, India; [4]Department of Radiodiagnosis, Tata Memorial Hospital, Mumbai 400012, Maharashtra, India; [5]Department of Radiotherapy, Tata Memorial Hospital, Mumbai 400012, Maharashtra, India; [6]Department of Nuclear Medicine, Tata Memorial Hospital, Mumbai 400012, Maharashtra, India; [7]Department of Pathology, Tata Memorial Hospital, Mumbai 400012, Maharashtra, India

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Abstract: Central nervous system (CNS) involvement in Hodgkin lymphoma (HL) is an extremely rare presentation with dismal outcomes according to reported literature. An 8-year-old girl presented to us with complaints of on-off fever, right cervical swelling and bilateral ptosis. Positron emission tomography (PET) showed intracranial extra-axial soft tissue masses in right infero-lateral temporal lobe, sella and bilateral parasellar region along with cervical, mediastinal, axillary, abdominal and inguino-pelvic nodes, liver lesions and extensive marrow lesions involving the axial and appendicular skeleton. Histopathology of the cervical lymph node revealed a diagnosis of classical Hodgkin lymphoma. Child received 2 cycles of OEPA and 4 cycles of COPP followed by radiotherapy to bulky cervical lymph nodes and intracranial lesion. The child has been disease-free for 44 months with no neurological sequalae. Intracranial spread is rare in Hodgkin lymphoma and is associated with inferior outcomes. Due to its rarity, there are no specific treatment guidelines for this entity. The choice of ideal chemotherapeutic agents and role of whole-brain radiotherapy needs further evaluation.

Keywords: Hodgkin lymphoma, central nervous system, intracranial, pediatric

Introduction

Central nervous system (CNS) involvement in Hodgkin lymphoma (HL) is an extremely rare presentation with dismal outcomes according to reported literature. Management includes a combination of chemotherapy and radiotherapy though no standard treatment guidelines exist. We herein describe our experience with an 8-year-old girl with HL who presented with CNS involvement in addition to generalized lymphomatous involvement.

Case

An 8-year-old girl presented to our outpatient department with complaints of on and off undocumented fever for 1 year and gradually progressive right neck swelling for 3 months. Physical examination revealed a firm right cervical lymph nodal mass with no other peripheral lymphadenopathy or hepatosplenomegaly. On neurological assessment, she had bilateral ptosis with mid-dilated pupils and sluggish bilateral pupillary reaction. Her baseline complete blood count showed a haemoglobin of 10.4 g/dl, total leucocyte counts of $15.16*10^9$/L and platelet count of $714*10^9$/L. Baseline LDH was 391 U/L (Normal range - 110-295 U/L), and renal function tests and liver function tests were within normal limit with no evidence of tumour lysis syndrome.

A contrast-enhanced computed tomography (CECT) was done for evaluation of the ptosis which revealed extra-axial lobulated soft tissue

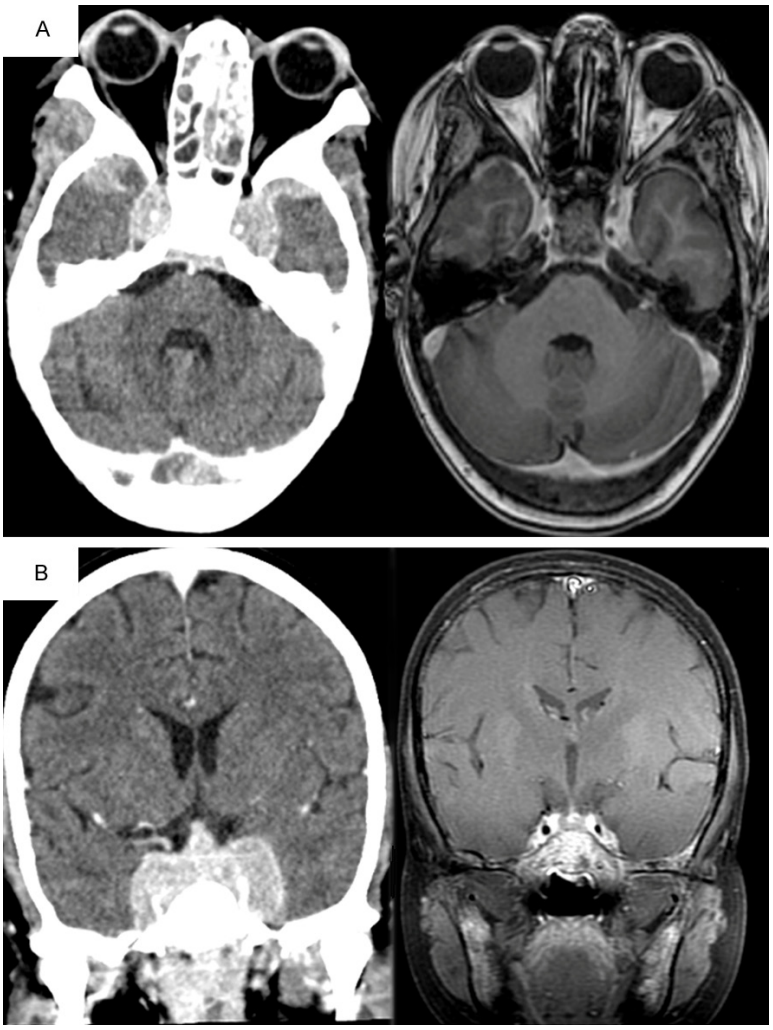

Figure 1. Baseline CECT of the brain showing dura-based soft lesions with complete resolution in end-of-treatment MRI in (A) axial and (B) coronal section.

masses in bilateral parasellar region involving the dura matter and the cavernous sinuses, and encasing the cavernous segment of bilateral internal carotid arteries (**Figure 1**). The mass indented both the temporal lobes with no obvious infiltration or oedema of the brain parenchyma. Superiorly it extended into the sella and along the pituitary stalk. Posteriorly the mass extended into the prepontine cistern along the clivus. A similar soft tissue was seen posterior to the Torcula of Herophili. The mass appeared mildly hyperdense on non-enhanced CT scan and showed homogeneous enhancement after administration of intravenous contrast.

The most probable differential diagnosis for a cervical lymph nodal mass with intracranial lesions was non-Hodgkin lymphoma (NHL), though duration of symptoms did not support the same. Hence, the child received prophase COP (Cyclophosphamide, Vincristine and Prednisolone) with dexamethasone in place of prednisolone while awaiting histopathology report and a bone marrow aspiration along with biopsy and lumbar puncture with intrathecal cytarabine administration, was done, considering an initial possibility of NHL. Histopathological examination of the cervical lymph node revealed large, atypical cells which were positive for CD30, GATA3 and weakly positive for PAX-5, while being negative for CD15, EBV-LMP1, ALK-1, CD1a and CD20, with preponderance of T-lymphoid cells in the background, suggestive of Hodgkin lymphoma. Staging PET CECT showed multiple FDG (fluorodeoxyglucose) avid homogenously enhancing solid intracranial extra-axial dura-based lesions along the right infero-lateral temporal lobe, the sella, bilateral parasellar region along the cavernous sinuses and posteriorly along the occipital lobe with maximum SUV (standardized uptake values) of 10.99. Contiguous medullary involvement of the bones of skull base was noted along with extramedullary extension into the right masticator space involving the temporalis muscle and bilateral lateral pterygoids. The scan also showed FDG avid nasopharyngeal thickening, multiple FDG avid bulky cervical nodes (6.7*4.4*3.4 cm) along with mediastinal, axillary, abdominal, inguinal and pelvic nodes, liver lesions and extensive marrow lesions involving the axial and appendicular skeleton, indicating disseminated lymphomatous disease with intracranial extra-axial involvement (**Figure 2**).

Bone marrow aspirate and cerebrospinal fluid were uninvolved on morphology, but bone mar-

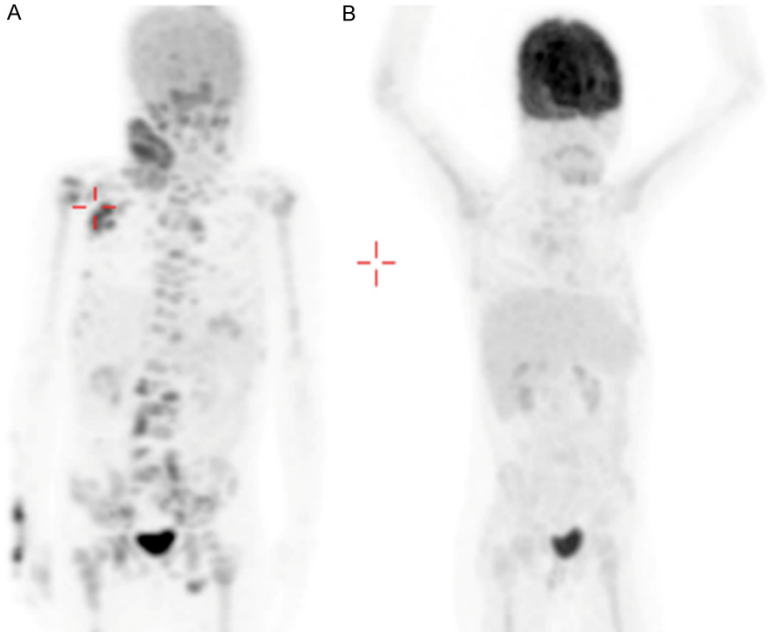

Figure 2. PET images showing disease burden at (A) Baseline and (B) after 2 cycles of chemotherapy.

row biopsy suggested involvement with Hodgkin lymphoma. So, the disease was staged as IVBX and risk stratified as high risk. Although as per institutional policy based on the Euronet PHL C1 protocol [1], patients with high risk Hodgkin Lymphoma received 2 cycles of OEPA [Vincristine (1.5 mg/m^2 on D1, D8 and D15), Etoposide (125 mg/m^2 on D1-D5), Prednisolone (60 mg/m^2 D1-D15) and Adriamycin (40 mg/m^2 on D1 and D15)] followed by 4 cycles of COPDAC [Cyclophosphamide (500 mg/m^2 on D1 and D8), Vincristine (1.5 mg/m^2 on D1 and D8), Prednisolone (40 mg/m^2 D1-D15) and Dacarbazine (250 mg/m^2 D1-D3)]. Our patient received first cycle as COPP [Procarbazine (100 mg/m^2 D1-D15) in place of Dacarbazine of COPDAC], in view of poor baseline nutritional status which increases the risk of severe toxicities of OEPA. Dacarbazine of the usual chemotherapy backbone was replaced with Procarbazine despite being gonadotoxic as the latter crosses the blood brain barrier [2]. A response PET was done after two cycles of chemotherapy (COPP+OEPA) which showed adequate response at all sites including the intracranial sites with a Deauville score 2. Following this, the child received one cycle of OEPA and three cycles of COPP. Magnetic resonance imaging (MRI) done at the end of chemotherapy showed complete resolution of intracranial soft tissue masses.

Our institutional guidelines mandate irradiation of bulky sites (peripheral lymph node with size ≥6 cm in any dimension). Hence, after completion of chemotherapy, patient received adjuvant image-guided intensity modulated radiation therapy (IG-IMRT) to the pre-chemotherapy extent of the intracranial lesion and right hemi-neck to a dose of 25.2 Gy in 14 fractions. She has been disease-free for 44 months now with no residual neurological deficit and without any late toxicities of chemotherapy or radiotherapy.

Discussion

Intracranial involvement in Hodgkin's Lymphoma is a rare occurrence with recent data from the German Hodgkin Study Group reporting a frequency of less than 0.02% [3]. Less than 100 cases of intracranial involvement in Hodgkin Lymphoma have been reported in literature so far, pediatric occurrence being rarer [4-8]. It is more commonly seen in the setting of disease relapse or late complication of poorly controlled systemic disease [5]. Both intra-axial and extra-axial metastasis have been described as intracranial presentation of Hodgkin Lymphoma. Hirmiz et al. did a pooled review of all cases of CNS Hodgkin disease reported in literature till then (n=36) and found brain parenchyma (64%) to be a commoner site of involvement in comparison to the dura (19%), corpus callosum (3%) and pituitary (3%) [10]. Intracranial metastasis commonly present as cranial nerve palsy, focal neurological deficit, headache, papilledema, coma and focal seizures. The predominant histological subtype reported with CNS disease in Hodgkin Lymphoma is mixed cellularity. Intracranial spread can occur through direct spread from the dura or osseous deposits or leptomeningeal spread or by direct extension from para-cranial or paraspinal lymph node involvement [5].

The rarity of CNS metastasis in Hodgkin Lymphoma has been attributed to the large size of the Reed-Sternberg (R-S) cells which makes the CNS impervious to them. The lack of

extravasation of the R-S cells is also attributed to the filtering effect of the lung and the intrinsic nature of the cells [8, 11, 12]. Being an uncommon presentation, histopathological confirmation is always recommended especially at relapse. Other common differentials including meningioma and NHL need to be ruled out in the setting of isolated CNS disease. Leptomeningeal disease is more commonly reported in widespread systemic disease and immunocompromised patients. PET findings in CNS involvement of lymphomas are mainly described in NHL, where CNS disease in known to be very avid (>2.5 times the grey matter) and studies have shown the use of PET SUV_{max} values in guiding diagnosis in these cases with reasonable sensitivity and specificity [13]. Role of functional imaging in patients with CNS deposits of Hodgkin Lymphoma is unclear; MRI remains the imaging modality of choice for characterization of these lesions.

To the best of our knowledge, there are 7 cases of intracranial disease in pediatric Hodgkin lymphoma, reported so far in literature, which are summarized in **Table 1**. All of them had intracranial disease in relapse setting. Ours is by far the first report of CNS involvement in de novo pediatric Hodgkin lymphoma. Though there are no guidelines for the management of intracranial disease in Hodgkin Lymphoma, most of the reported literature has described use of multimodality treatment including chemotherapy, surgery and radiotherapy [4-8]. With the advent of modern chemotherapy regimens, surgery can be reserved for cases with large intracranial mass causing compression of brain parenchyma and risk of brainstem herniation. Chemotherapy regimens comprising of drugs with CNS penetration like Lomustine, Carmustine and Procarbazine have been employed in various reports, some have also used intensive chemotherapy backbones like MIED [high-dose methotrexate (8 gm/m^2), Ifosphamide, Etoposide and Dexamethasone], ICE (Ifosphamide, Carboplatin and Etoposide) and high dose methotrexate. Intracranial methotrexate can be used in cases with meningeal disease though routine CNS prophylaxis is not recommended in Hodgkin lymphoma. There also have been reports of use of high-dose chemotherapy with autologous stem cell rescue in multiply relapsed setting [6].

Role of consolidative radiotherapy and its extent is another area of debate in this rare disease. Most of the earlier reports have described the use of whole brain radiation therapy (WBRT) along with boost to the gross disease to a total dose of 30-50 Gy [6, 14] in patients with intracranial spread of Hodgkin Lymphoma. There have been subsequent reports of complete remission with focal radiation to the gross disease (without WBRT) in intracranial relapse of HL. The International Lymphoma Radiation Oncology Group (ILROG) guidelines [15] recommend irradiating the whole organ in primary extra-nodal lymphoma. However, this recommendation is mainly based on experience with NHL considering the rarity of intra-cranial HL.

Das et al. [9] reported sustained remission in intra-axial CNS disease in relapse HL with the use of high-dose methotrexate-based chemotherapy and no radiotherapy. Akyuz et al. [6] reported three pediatric cases with intracranial Hodgkin disease at relapse, two had extra-axial lesions while only one had intra-axial disease. All three cases received salvage chemotherapy and WBRT. Though all these patients achieved initial response after completion of chemotherapy, none of them survived. Our patient with extra-axial CNS Hodgkin Lymphoma in upfront setting has been disease free with no neurological sequelae for 3 years now without the use of whole brain radiotherapy. These findings imply that use of CNS penetrating chemotherapy is more crucial in management of CNS lesions of Hodgkin Lymphoma while role of WBRT remains questionable.

Though literature on prognosis of Hodgkin lymphoma with intracranial involvement is scarce, previous reports have shown inferior outcomes with a median survival of 46 months, where all patients received radiotherapy with or without chemotherapy which is contrary to the recent report by Das et al. which has shown a longer progression free survival. Our patient continues to be in remission for 44 months now.

To conclude, incorporation of CNS-directed therapy in standard regimens for Hodgkin lymphoma can help in achieving better response rates and probably better outcomes. Use of consolidative radiotherapy needs to be re-evaluated especially in cases with an adequate interim response on imaging.

Table 1. Summary of selected reported cases of intra-cranial Hodgkin lymphoma

Study	Age/ Sex	Upfront/ Relapse (Number)	Site	Intra-axial or Extra-axial	Surgery Y/N	Chemotherapy Y/N	Chemotherapy Regimen	Radiation Y/N	Field	Relapse Y/N	Alive/ Dead
Akyuz [6] (2005)	15/F	Relapse (2nd)	Left parieto-occipital and Right parietal region No other systemic lesions	Intra-axial	N	Y	CCNU	Y	WBRT 4000 cGy with boost 2000 cGy	Y	Dead
Akyuz [6] (2005)	4/F	Relapse (3rd)	Right temporal lobe Dural involvement in left posterior parietal region Bone marrow biopsy involved	Intra-axial Extra-axial	N	Y	Cisplatin + Etoposide	Y	WBRT 3000 cGy with boost 1000 cGy	Y	Dead
Akyuz [6] (2005)	12/M	Relapse (2nd)	Left parietal dura-based	Extra-axial	N	Y	ABVD	Y	WBRT	Y	Dead
Sapozink [5] (1983)	11.5/M	Multiple relapses			Y	Y	CCNU, Glucocorticoids	Y	WBRT 3000 cGy	Y	Dead
Gupta [16] (2006)	5/M	Relapse (1st)	Left occipital dura-based	Extra-axial	Y	Y	ABVD	N (Planned but refused)		N	Alive
Balweirz [17] (1993)	7/M	Relapse (1st)	CSF suggestive of pleocytosis with multiple RS cells	-	N	Y	3 cycles of chemotherapy (backbone unknown) + Triple intrathecal therapy	Y	WBRT (18.2 Gy)	N	Alive
Das [9] (2016)	15/M	Relapse (1st)	Right basi-frontal region	Intra-axial	Y	Y	6 cycles of high-dose methotrexate (8 gm/m^2), Ifosphamide, Etoposide and Dexamethasone (MIED)	N	-	N	Alive

ABVD-Adriamycin, Bleomycin, Vinblastine, Dacarbazine, CCNU-Lomustine, CSF-Cerebro-spinal fluid, RS cells-Reed-Sternberg cells, MIED-High dose methotrexate, Ifosphamide, Etoposide and Dexamethasone, WBRT-Whole brain radiation therapy.

Disclosure of conflict of interest

None.

Address correspondence to: Nirmalya Roy Moulik, Division of Pediatric Oncology, Department of Medical Oncology, Tata Memorial Hospital, Dr. E. Borges Road, Mumbai 400012, Maharashtra, India. Tel: +91-7045991385; E-mail: roymoulik@gmail.com

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