Intracerebral Langerhans cell histiocytosis treated with low dose Radiation alone: report of a rare case and review of the literature


Abstract
Cerebral Langerhans cell histiocytosis (LCH) is a rare granulomatous disorder which may be primary, secondary and solitary or multiple. Central Nervous System (CNS) involvement without a systemic disease is very rare. The most frequent involvement of the cerebral LCH is in the cranial bones and the hypothalamic-pituitary axis (HPA). Cerebral LCH without involvement of HPA is very rare. We have brought into focus the biology and treatment options of this rare tumor by citing a case of intracerebral LCH (involving periventricular, parenchymal, midbrain, external capsule, and putamen) without involving HPA in a 10-year-old boy. He was treated successfully with radiotherapy. A short review of the relevant literature is also presented. We have also outlined the biology and the therapeutic options of this enigmatic tumor.

Keywords: Intracerebral LCH, LCH, histiocytosis

Introduction
Langerhans cell histiocytosis (LCH) is a rare systemic granulomatous disease characterized by single or multiple osteolytic bone lesions with variable clinical course [1]. Cerebral LCH may be primary or secondary. Involvement of brain structures outside the hypothalamic-pituitary axis (HPA) is even rare. The treatment of such tumors is poorly defined. Herein we intend to report a case of intracerebral LCH in a 10-year-old boy, treated successfully with radiotherapy. We also present a short review of the literature.

Case Report
A 10 year old boy presented to our outpatient department with two years history of recurrent headache. He had no associated vomiting, visual disturbance or seizures. The boy had an ECOG (Eastern Cooperative Oncology Group) performance status of zero. On clinical examination, no abnormality was noted in the higher function test. There were no evidence of cranial nerve palsy or sensory-motor deficit. Cerebellar functions were also not altered. Visual acuity in both eyes was normal. A Gadolinium-enhanced magnetic resonance imaging (MRI) of the brain revealed homogenously enhancing conglomerate lesions in right peri-ventricular region, putamen, and external capsule, left middle and anterior frontal lobe showing choline and lipid peak with associated peri-lesional edema. There were few lesions on the right parietal skull vault. There was no evidence of calcification, hydrocephalus and midline shift (Fig: 1A-1D). The patient underwent biopsy from the left parietal lobe lesion which revealed a collection of large polygonal to oval cells with eosinophilic to clear cytoplasm and vesicular nuclei. There was marked reactive gliosis. Intermixed lymphocytes were also noted. The large cells were immuno positive for CD68, S100 and langerin (focally) (Fig 2A-1D); while immuno negative for Glial fibrillary acidic protein (GFAP) and CD1a, suggestive of LCH. Bone scan revealed focal tracer uptake in the right parietal bone and bilateral temporal bones only. Whole body FDG PET CT scan showed increased osteoblastic activity and mild FDG uptake in the subtle osteolytic lesions in the right parietal and bilateral temporal bones. Few intensely FDG avid hyper dense parenchymal lesions were noted involving the left frontal, right ganglio capsular, right basi-frontal regions and in the left side of midbrain with mild peri-
lesional edema. There was no evidence of systemic diseases and endocrine functions were within normal limits. A final diagnosis of Langerhans cell histiocytosis with gross involvement of cerebral parenchyma was made. Since the tumor was deemed surgically un-respectable, the patient was treated with whole brain radiotherapy to a dose of 12 Gray in 6 fractions over 6 days. The entire brain parenchyma and skull was considered the clinical target volume and a 5 mm isotropic expansion was added to form the planning target volume. Radiation was planned by three-dimensional conformal technique (3DCRT) in the Eclipse treatment planning system (version 6.5) with two coplanar fields (right and left lateral skull) using 6 MV photon beams. The patient tolerated treatment well without major toxicity or unplanned treatment break. We have reserved the chemotherapy for salvage. Follow up MRI brain at 3, 6 months and 1 year post radiotherapy, showed near total resolution of perilesional edema, more than 50% reduction in size of the lesion suggestive of good response (Fig 1E-1G). The patient improved symptomatically. He is neurologically intact and radiologically stable at the last follow up.

Fig 1 A to 1D: Pre Radiotherapy Gadolinium-enhanced MRI shows homogenously enhancing conglomerate lesions in peri-ventricular region, putamen, and external capsule (A) Tumor is hyperintense on T1W axial section, (B) hyperintense on T2 W axial section with significant perilesional edema (arrow), (C) edema is better demonstrated on FLAIR (D) Sagital image showing conglomerate periventricular lesion with significant edema.

Fig 1 E to 1G: Post Radiotherapy MRI showing (E) enhancing foci in right external capsule and right peri-ventricular region in T1W axial section (F & G) T2W and sagital section shows significant resolution of lesion with no edema.

Fig 2: Shows a tumor composed of oval to polygonal cells and reactive gliosis in periphery (A. HE X200) along with osteoclast like giant cells and (arrow) mixed inflammatory infiltrate (B. HE X200). These cells have abundant eosinophilic cytoplasm with vesicular nuclei. Background reveals few scattered eosinophils and lymphocytes (C. HE X400). The cells were immunopositive for CD68 (D. IHC X200), S100 (E. IHC X200) and focal for Langerin (F. IHC X200).

Discussion and review of literature
LCH is a rare histiocytic disorder commonly characterized by single or multiple osteolytic bone lesions demonstrating infiltration with histiocytes. CNS involvement without systemic disease is very rare. Approximately one percent of LCH patients develop mass lesions or granulomas in the brain parenchyma or choroid plexus [2]. The most common manifestations of CNS involvement are symptoms of diabetes insipidus (DI) and neuro-degeneration (ataxia, cognitive dysfunction) [3]. However, presentation varies with the location of bone involvement. The most frequent presentation of CNS LCH is involvement of the cranial bones and the HPA with DI as key manifestation [4]. The second most frequent presentation is a combination of pathologic changes in the cerebellum, basal ganglia, and/or Pons. Space occupying lesions occurs very rarely, temporal lobe being the commonest, followed by the frontal lobe and the parietal lobe. Only 22 cases of solitary LCH involving brain parenchyma have been reported till date.
They consisted of 15 males and 7 females with a mean age of 28.5 years (range, 3-40 years). The findings suggested that the cerebral LCH tends to occur later than that of other systems. The temporal lobe was involved most commonly, followed by the frontal lobe and the parietal lobe. Of all the 22 patients, 2 cases of recurrence have been reported, and one of them died from the disease.

On imaging, there is no characteristic pattern for intra-cerebral LCH. These lesions have been described as low-density masses with surrounding edema on CT and MRI. Gabby et al. noted that space occupying lesions are typically characterized by signal intensity corresponding to soft tissue, presenting intermediate intensity on T1-weighted images (T1WI) and T2-weighted images (T2WI) with moderate or marked homogeneous enhancement. The two common patterns noted for white matter changes are peri-vascular pattern and a leukoencephalopathy pattern. The leukoencephalopathy-like pattern involves the Cerebellar white matter, the Pons, and the periventricular white matter and presents with symmetric patchy areas characterized by high signal intensity on T2WI and low signal intensity on T1WI without a clear vascular distribution. In our reported case MRI revealed homogeneously enhancing conglomerate lesions in periventricular region, putamen, external capsule, left middle frontal lobe, anterior frontal lobe and right parietal skull vault showing increased Choline and lipid peak.

The final diagnosis should be made by pathological features. Biopsies of involved tissue usually demonstrate heterogeneous collections of Langerhans cells with eosinophils, neutrophils, small lymphocytes, and histiocytes (which may form multinucleated giant cells). Morphologically, Langerhans cells are large oval mononuclear cells with few cytoplasmic vacuoles, little or no phagocytic material, and moderately abundant, slightly eosinophilic cytoplasm. The nucleus is prominent with fine chromatin and thin nuclear membranes imparting a “twisted towel” or “coffee bean” appearance. LCH express the histiocytic markers CD1a, S100, and CD207 (langerin) and contain Birbeck granules. CD1a is usually positive in LCH but there have been instances of CD1a negativity that still count because of S100 and langerin. In our reported case LCH was diagnosed based on S100 and langerin. Grois et al. mentioned three different types of lesions: (i) circumscribed granulomas within the brain’s connective tissue space, such as meninges or choroid plexus (ii) granulomas within the brain’s connective tissue spaces with partial infiltration of the surrounding CNS parenchyma and (iii) neurodegenerative lesions, mainly affecting the cerebellum and the brainstem. Optimal treatment for LCH with CNS mass lesions is not yet well defined and depends on the site of the disease. Only a few series with small numbers of patients or cases have been published. The quality of the treatment data on the patients with CNS disease was very heterogeneous. Treatment options for space occupying lesions which are surgically unresectable are very limited. Grois et al. suggested that the tumors arising from intracranial regions other than the hypothalamic pituitary axis, should be treated with combined modalities, including surgery, radiation, or chemotherapy. Tin et al. suggested vinblastine, with or without steroids, could potentially be a useful therapeutic option in LCH, especially for those with inoperable lesions or multiple lesions, but little is known about its efficacy with CNS mass lesions. In the absence of adequate data chemotherapy is used only when multiple organs are involved.

In our reported case, since lesions involved periventricular, parenchymal, gangliocapsular and part of midbrain, it was surgically unresectable. So we have treated with whole brain radiotherapy alone. The potential side effects of whole brain radiotherapy are diminished neuro-cognitive functions, endocrine dysfunction and diffuse white matter injury. After one year post radiotherapy the patient was clinically stable without neurological symptoms and significant resolution of the intra-cerebral mass. We are planning to follow up the patient with serial imaging. We decided to reserve chemotherapy for salvage in case of disease progression.

Conclusion

LCH has rarely been reported to primarily involve the brain parenchyma. Even, in patients with bone diseases it appears to involve the HPA only. Cerebral parenchymal involvement outside the HPR is extremely rare. This present case is a rare example of such parenchymal involvement with minimal bone disease. We would like to highlight the importance of radiotherapy in conferring disease control.

References