CASE REPORT ON LANGERHANS CELL HISTIOCYTOSIS

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ABSTRACT

BACKGROUND

Langerhans Cell Histiocytosis (LCH) is a rare proliferative disorder, in which pathological Langerhans Cells (LCs) accumulate in a variety of organs. The clinical spectrum of disease ranges from the chronic, localised form to an acute leukaemia-like disease with a fatal outcome. Herein, we report a case who presented with swelling in the frontal region and diagnosed as Langerhans Cell Histiocytosis.

KEYWORDS

Histiocytosis, Langerhans.

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BACKGROUND

LCH previously has been considered as a reactive polyclonal disease of immune regulation and not a true neoplasm. More recent evidence however has demonstrated clonal proliferation, a key neoplastic feature.[1-2] LCH afflicts young children primarily, some adolescents and a few young adults. The classic presentation involves lytic lesions of bone, particularly of the skull.[3] The pathophysiology of LCH involves histiocytes- cells derived from monocytes of the granulocyte/macrophage series after extravascular diapedesis. Histiocytes function either as antigen-processing cells, phagocytic cells or as antigen-presenting cells.[4] Langerhans' cells are specialised histiocytes with immune functions similar to other dendritic cells and macrophages. Langerhans' cells function immunologically by presenting antigen to T lymphocytes.[5] In LCH, these cells undergo pathologic change and appear histologically within an inflammatory background with a varied microscopic appearance that necessitates additional analysis in order to establish a diagnosis.[6,7] Histological presence of Langerhans' granules (also called Birbeck's granules. Birbeck's granules are rod-shaped ultrastructural organelles that may have a vesicular portion giving it a so called "tennis racquet" appearance under electron microscopy. The presence of Birbeck's granules is pathognomonic of LCH.

CASE REPORT

A 5-year-old male child presented with complaints of swelling in the skull on the right frontal region since 2 months which was progressive measuring around 3 * 3 cm, single and non-tender, cystic, not associated with blurring of vision, headache or skin involvement. There was no hepatomegaly or lymphadenopathy on examination.

Systemic examination was normal. Eye examination and hearing was normal. CBC, LFT, RFT and CXR were normal. FNAC report was suggestive of Langerhans Cell Histiocytosis. CT brain showed extracranial hypertense soft tissue lesion on the right frontoparietal region in both the outer and inner table of the skull with calvarial defect and mild compression of the brain parenchyma. Right frontal craniectomy with gross total excision of the tumour with dural repair was done. Tissue was sent for histopathological examination and was suggestive of Langerhans Cell Histiocytosis.

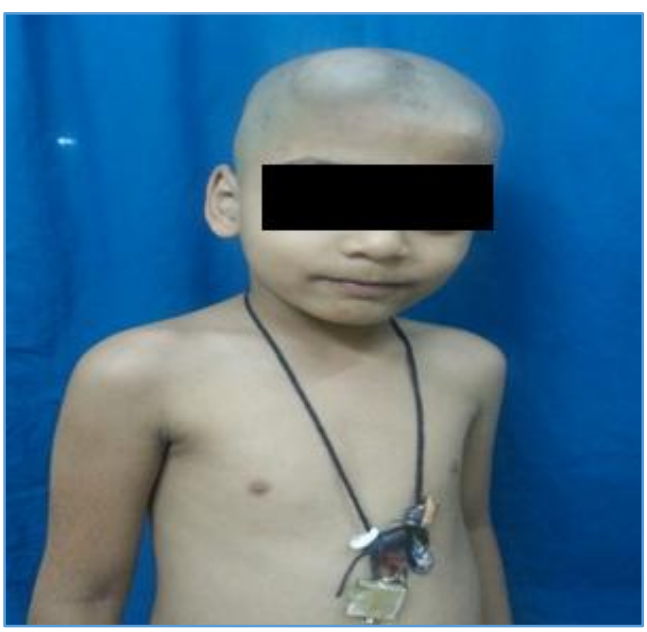

Figure 1. Swelling noted in the scalp in the Right Frontal region

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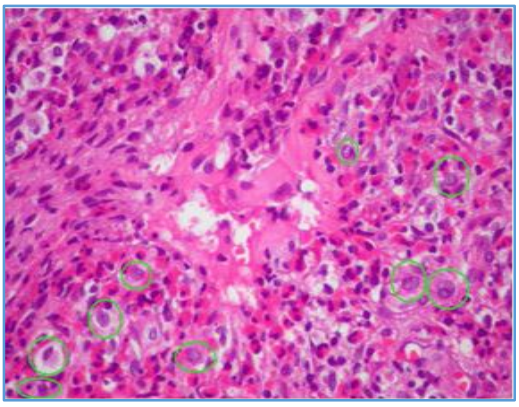

Figure 2. Histopathological Examination of the Specimen demonstrating Bribeck granules

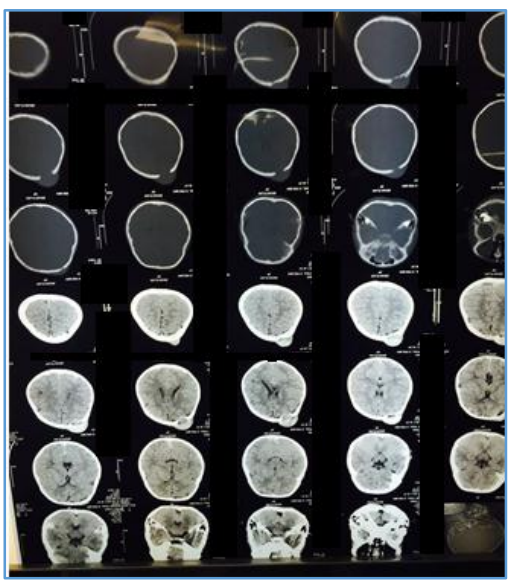

Figure 3. CT brain showing Extracranial Hyperintense soft tissue lesion in the right frontoparietal region in both the inner and outer table with Calvarial defect with compression of the brain Parenchyma

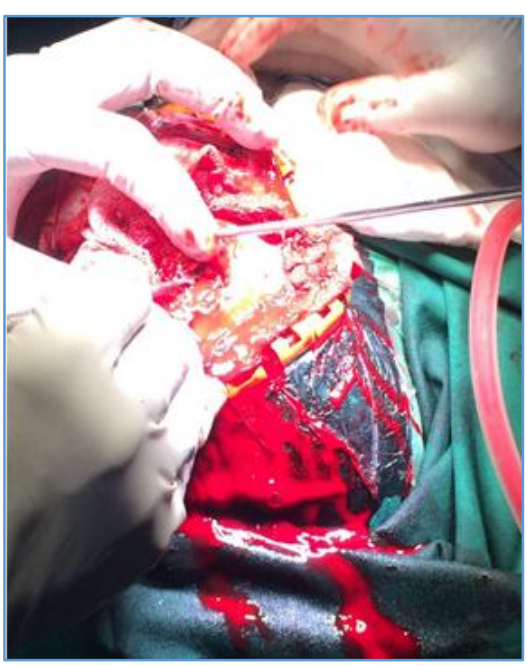

Figure 4. Intraoperative image of right frontal Craniectomy with gross total excision of the Tumour with dural repair

DISCUSSION

The generic term "histiocyte" refers to several types of cells including: monocytes/macrophages, dermal/interstitial dendritic cells and Langerhans Cells (LCs). In the past, there had been a great deal of confusion as to how to classify the histiocytoses since the exact ontogeny was not completely understood. However, with the advent of immunohistochemical stains the Histiocyte Society proposed reclassification of these disorders based upon the predominant cell type in the infiltrate. This initial classification system included Langerhans histiocytosis (Class I), non-Langerhans cell histiocytosis (Class II) and malignant histiocytosis (Class III).[8] As more information has become available, a revised classification scheme was proposed and includes dendritic cell disorders, macrophage-related disorders and lastly malignant histiocytic disorders.

One of the more common histiocytoses is LCH, which occurs as a result of a monoclonal proliferation of the pathological LC in a variety of organs including the skin. Although, the cells seen in LCH closely resemble normal LC, they appear more immature (expressing CD14), less dendritic and more mitotically active (approximately 3 - 48% cells are in division), but possess reduced to absent antigen-presenting capability.

Historically, LCH was sub-categorised eponymously based upon the different clinical manifestations. However, with the advent of ultrastructural studies and immunohistochemical stains, conditions that were once believed to be separate entities have been unified under the rubric of LCH. Included in this category are conditions that were previously designated as eosinophilic granuloma, Hand-Schüller-Christian disease, Letterer-Siwe disease, histiocytosis X, pure cutaneous histiocytosis, congenital self-healing reticulohistiocytosis, Hashimoto and Pritzker disease, Langerhans-cell granulomatosis, type II histiocytosis and the generic term non-lipid reticuloendotheliosis.

LCH has an extremely variable presentation. The incidence of LCH ranges from 0.5 to 5.4 cases per million persons per year, depending upon the age of the population investigated. Clonality of the proliferating cells has been cited to support the concept of a neoplastic process; however, clonality does not necessarily imply malignancy and can be seen in benign reactive processes. The LCs in LCH manifest an activated immunophenotype, resulting in their increased proliferation and migration. Aberrant or uncontrolled cytokine production by these inflammatory cells likely results not only in further proliferation of LCs, but also contributes to the pathological sequelae of LCH including fever, fibrosis, bone resorption and necrosis. Although no clear aetiology has been identified, the general consensus is that patients with LCH have a dysregulated immune response with failed transition from "innate" to "adaptive" immunity. [Langerhans cell histiocytosis may involve almost any organ system, but the frequency of involvement as well as the extent of the disease is often age dependent. The skeleton is involved in 80% of patients and may be the only affected site. Bone lesions may be single or multiple and are seen most commonly in the skull.

They may be asymptomatic or associated with pain and local swelling. Exophthalmos when present often is bilateral and is caused by retro-orbital accumulation of granulomatous tissue. The cornerstone of diagnosis in LCH includes identification of the characteristic clinical features, but also

requires corroborating histopathological and immunohistochemical findings. The clinical course of single-system disease (usually bone, lymph node or skin) generally is benign with a high chance of spontaneous remission. Single system disease has high remission rates. The cornerstone of diagnosis in LCH includes identification of the characteristic clinical features, but also requires corroborating histopathological and immunohistochemical findings. A presumptive diagnosis of LCH can be made based upon light microscopic findings and a compatible clinical picture; but a definitive diagnosis requires that the lesional cells exhibit positive staining with S-100 and CD1a. Although, CD1a is fairly specific, it also labels cortical thymocytes and interdigitating dendritic cells within the dermis and lymph nodes. Despite the fact that TEM is the "gold standard," this technique is rarely performed today because immunohistochemical stains have become widely available, easy to use and relatively inexpensive. Furthermore, the number of LCs with identifiable Birbeck granules can vary depending upon the type of tissue sampled: limited numbers are visualised in biopsies taken from lesional tissue from the liver, spleen, gastrointestinal tract and central nervous system. Therefore, other pathognomonic surface markers are being sought. Langerin (CD 207) is a relative new monoclonal antibody directed against a type II transmembrane protein associated with Birbeck granules. It appears to be more sensitive and specific for LCs than CD1a. In the future, it may be a key component of an immunocytochemical panel to identify LC.

The Histiocyte Society has established a set of guidelines to assist in the diagnosis and study of LCH.[9] The initial evaluation consists of a complete physical examination inclusive of height and weight measurements in addition to laboratory studies including haematological assays and coagulation studies, liver function tests and urine osmolality. Although, some authorities advocate bone marrow examination in every baseline examination, it is not required unless symptoms or blood tests suggest involvement. Lastly, the patient must have a complete skeletal radiographic survey and chest radiography. Patients with identified abnormalities require more specific studies, such as pulmonary function tests and lung biopsy, small bowel series, liver biopsy, panoramic dental films, CT or MRI of the brain with particular attention paid to the hypothalamic-pituitary axis, endocrine evaluation and otolaryngology consultation with audiogram. Since patients with LCH often have chronic and recurrent disease, followup studies are required every month to 6 months depending upon organ system involvement and the degree of organ dysfunction.[9]

Within the last 20 years several multi-centre, randomised therapeutic trials have contributed to a more uniform treatment approach. For patients who have localised bone lesions, curettage is generally sufficient for diagnosis as well as therapy, although some cases may require intralesional steroids or low dose radiation. For patients who have localised bone lesions, curettage is generally sufficient for diagnosis as well as therapy, although some cases may require intralesional steroids or low dose radiation. Curettage and local radiation therapy can be used as treatment options. Multisystem disease is treated with multidrug chemotherapy with vinblastine and etoposide. If unresponsive immune-suppressive agents are started, stem cell transplantation can also be done.

Despite adequate treatment, it has been shown that survivors of LCH have long-term sequelae, some of which may not become apparent until many years later. One retrospective study analysed patients who had been treated for multi-organ system LCH and found that 75 percent had detectable long-term sequelae such as hypothalamic-pituitary dysfunction (50%), cognitive dysfunction (20%) and cerebellar involvement (17.5%).[10] Some sequelae are multifactorial. For example, growth retardation can occur as a result of gastrointestinal involvement by LCH, thereby resulting in malabsorption or due to deficiencies in growth hormone from anterior pituitary lesions or from the residua of chemotherapy. Furthermore, long-term complications are not limited to patients with multi-organ system disease and approximately 25 percent of patients with single-system disease experience permanent sequelae.[11] Even patients diagnosed with congenital self-healing LCH have been shown to have late relapses and/or progression to systemic disease. Consequently, all patients with LCH require long-term follow-up to identify disease recurrence or late-stage complications.

To aptly determine a patient's prognosis and treatment protocol, it is currently recommended that patients are risk-stratified based upon the number of organs involved and degree of organ dysfunction. Patients diagnosed with organ dysfunction are further stratified based upon which organ system is involved. Patients with involvement of the spleen, lung, liver or haematopoietic system often have a worse prognosis.

CONCLUSION

In summary, LCH represents a disease with a diverse spectrum of clinical manifestations. Herein through this case, we summarise the current recommendations of the Histiocyte Society regarding the classification, evaluation, prognosis and treatment of LCH. Early suspicion of the disease should be thought of in view of varied presentation for effective and early initiation of treatment. A definitive diagnosis of LCH can be made by obtaining a biopsy that yields cells that are morphologically and immunohistochemically compatible with LCs. Proposals by the Histiocyte Society have assisted in the unification of LCH into one disease category and has allowed for more efficient treatment protocols to be designed via risk stratification. The prognosis depends chiefly upon the involvement of multiple organ systems, organ dysfunction and the patient's response to chemotherapy during the initial 6 weeks of treatment.

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