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Hemophagocytic Lymphohistiocytosis in a child with Gorlin Syndrome and Medulloblastoma – A Case report

Himani Dhingra [1], Varindera Paul Singh [2], Manas Kalra [3], Amita Mahajan [4*]

[1] MD Pediatrics, DNB Pediatrics, FNB Pediatric Hematoncolgy; Assistant Professor Pediatrics, SGT Medical college Hospital and Research Institute, Budhera, Gurugram, India.

[2] Mch Neurosurgery, DNB Neurosurgery; Senior Consultant Neurosurgery, Medantamedicity Hospital, Gurugram, India

[3] MD Pediatrics, DNB Pediatrics, FNB Pediatric Hematoncology; Senior Consultant Pediatric Hematoncology, Sir Gangaram Hospital, New Delhi, India

[4]MD Pediatrics, MRCPCH, CCST; Senior Consultant Pediatric Hematoncology, Indraprastha Apollo Hospital, New Delhi, India

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***Corresponding author:** Amita Mahajan, Department of PediatricHematoncology and BMT, Indraprastha Apollo Hospital, Delhi, India.

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening syndrome resulting from excessive but ineffective immune activation. Secondary HLH in children is most often associated with infection, autoimmune disease and malignancy. Malignancy associated HLH (MA-HLH) has predominantly been described in association withhematolymphoidmalignancy. It has very rarely been described in the setting of central nervous system (CNS) tumors. We report a caseofMedulloblastoma (MB) in a child with Gorlin syndrome, whose clinical course was complicated with HLH. Prompt diagnosis and treatment resulted in complete clinical resolution.

Key Words: HLH; malignancy; medulloblastoma; gorlin syndrome

Introduction

HLH is a potentially life-threatening syndrome caused by uncontrolled immune activation leading to excessive macrophage activity and cytokine release resulting in tissue damage and multi-organ dysfunction [1,2]. Primary/Familial HLH is caused by a defect in the gene encoding the molecules in the pathway of cytotoxic T lymphocytes (CTLs) and natural killer cells (NK) and is usually seen in early childhood or infancy [3]. Secondary HLH occurs more frequently and is usually secondary to infection, autoimmune disease, immunodeficiency ormalignancy [4] .

Secondary HLH is often difficult to diagnose, as clinical findings and investigations are nonspecific and may be difficult to differentiate fromthe underlying condition that triggers the immunological cascade. A high index of suspicion is needed for early diagnosis. The diagnosis of MA-HLH is even more challenging as signs and symptoms may overlap with the underlying malignancy or treatment associated complications. Up to 1% of adults with hematologic malignancies may be associated with HLH with high fatality rates [5]. MA-HLH in children has been reported less frequently [6-11]. Early recognition with prompt treatment is imperative to prevent adverse outcomes.

Case Presentation:

A 21 month old male child,presented with progressive enlargement of head size with increased irritability since 3 months. The child was not gaining developmental milestones as per age. There was also history of intermittent episodes of vomiting. On examination the head circumference was above 95th centile with prominent frontal bossing and coarse facial features. Cranial nerve examination was within normal limits and there were no signs suggestive of other motor neurological deficits. Mother also had striking facial features with enlarged forehead, maxillary prominence, mandibular hypoplasia and

receeding chin. There was history of prior surgery of lower jaw cyst in the mother with histopathology being consistent with a mandibular odontogenic keratocyst.

On further evaluation of the child, Magnetic Resonance Imaging (MRI) brain donerevealed amass in the fourth ventriclewith obstructive hydrocephalus. There was no evidence of spinal metastasis on imaging or cerebrospinal fluid (CSF) cytology. He underwent endoscopic 3rd ventriculostomy and microsurgical gross total excision of 4th ventricular tumour. Histopathological examinationof specimen was consistent with MB (WHO grade 4), desmoplastic nodular histology. Molecular studies confirmed Sonic Hedge Hog(SHH) activated MB with wild type TP53. Post operative MRI brain revealed no residual disease.

Forty eight hours post surgery he developed persistenthigh grade fever without any localizing signs. Blood and CSF cultures were repeatedly negative. Complete hemogram (CH) showed Hb-8.5g/dl , TLC 2080/cumm with 35% neutrophils and platelets 91,000/cumm.Extensive workup for infective causes did not reveal any etiology. Based on these clinical findings of hectic fever and pancytopenia in a background of malignancy differential diagnosis of HLH was suspected and he was evaluated for the same. Serum ferritin and triglyceride levels wereraised (2747 ng/ml and 246 mg/dL respectively).Plasma fibrinogen was 127mg/dL(ref range 150-400mg/dL).Bone marrow examination showedmacrophage activationand hemophagocytosisas shown in (fig.1).CSF analysis done on post operative day 6 showed few mature lymphocytes, neutrophils and occasional histiocytes. There was also CSF pleocytosis (White blood cells 140 with 65% neutrophils and 35% lymphocytes) with raised protein (188 mg/dL) but no hypoglycorrhachia (CSF glucose 65 mg/dL) .Based on these findings a diagnosis of HLH was made as perthe 2004 diagnostic criteria. Detailed work up for common infectious triggerslike Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) quantitative DNA PCR for secondary HLH was initiated but nothing conclusive was identified.He was commenced ondexamethasone (10 mg/m^2/day)monotherapy and had resolution of symptoms with improvement of biochemical parameters within 5 days. After clinical improvement systemic chemotherapy was initiated as per HIT SKK (HirntumorenSauglinge und Kleinkinder) protocolfor MB.Radiotherapy was omitted in view of the age of the child.
In view of the maternal history, characteristic facial features and SHH activated MB in the child, mutational analysis was sent for Gorlin Syndrome.Both mother and the baby showed pathologic mutations in PTCH1 gene. After 2 years 5 months since diagnosis patient continues to be well and symptom free on follow up.

Discussion:

MA- HLH has been rarely reported in children [6-11]. As in adults, the common triggers for MA-HLH are usually hematologic malignancies with solid tumoursbeingrarely implicated. To our knowledge, there are only two previous reports of MA-HLH in the setting of a CNS tumour in pediatric oncology bothbeing relapsed MB [6,10]. Coincedentally both the patients, as reported in these studies were less than 2 years of age, hadCMVas an infectious trigger and both succumbed to HLH. No infectious trigger was found in our patient and HLH was solely attributed to malignancy itself.

MA-HLH may manifest as the presenting feature of an undiagnosed malignancy or at any point during treatment. Several possible pathogenetic mechanisms have been proposed. Excessive secretion of proinflammatory cytokines and persistent antigenic stimulation by the tumor cells, triggering hyperinflammation is one of the probablefactors attributing to HLH at the initial presentation or at relapse of malignancy. MA-HLH may also occur during treatment. The immune dysregulation generated by the underlying malignancy and/or the treatment modalities like chemotherapy/ hematopoietic stem cell transplant may aggravate T-cell dysfunction, triggering HLH. Tumor directed therapies leading to myelosuppressionand immunosuppression predispose to infection, which may act as independent trigger of MA-HLH in these patients.In a 20 year single centre, retrospective review of MA-HLH in pediatrichemat-oncology patients Strenger et al [10], have differentiated the malignancy induced and the chemotherapy induced HLH as two different entities. In this series mostly patients developed HLH after starting antineoplastic treatment. This was however in contrast to the series of patients described by Lehmberg et al [9] where majority of patients developed HLH secondary to malignancy itself.

More recently, symptoms similar to those observed in HLH have been described in patients receiving immunotherapies (eg.bispecific monoclonal antibody blinatumomab, chimeric antigen receptor T-cell therapies, dendritic vaccines, checkpoint inhibitors) and immunomodulatory drugssuch as lenalidomide and thalidomide [12,13]. The cytokine release syndrome (CRS)associated with these therapies bears a clinical and immunologic resemblance to that of HLH and often responds to the treatment used for the same.

Fever is a common symptom in pediatric oncology patients. However, persistent fever without localizing signs, not adequately responding to optimal antibiotic or antifungal treatment should raise a suspicion of HLH. Presence of cytopenia, hyperferritenemia, hypertriglyceridemia and/or hypofibrinogenemia may help corroborate the diagnosis. Prompt recognition and management is a prerequisite for a favorable outcome. It is unclear whether the current diagnostic criteria for HLH are best suited for early diagnosis of this entity. Daver et al [14] have suggested a 18 point criteria using clinical and lab parameters that are much more widely available for early diagnosis of MA-HLH in adults which is currently undergoing prospective validation (NCT02385110).

MA-HLH may have a varied clinical course and therefore the treatment needs to be individualized based on severity of symptoms. The therapeutic options involve witholding ongoing chemotherapy, commencing steroids, cyclosporin or initiating HLH directed chemotherapy in addition to identifying and treating the underlying infective triggers. As described by Strenger et al [10], mostly patients in their series improved with steroid monotherapy similar to our patient. However, another study [9] has reported requiring aggressive treatment modalities for MA-HLH patients with a median survival of 1.2 months and high fatality rate.

Conclusion:

MA-HLH is a rare but often fatal disease. Ahigh index of suspicion is often needed to suspect HLH in the background of malignancy.Early recognition and prompt treatment are the key to improve survival in this patient group.

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