Clinical approach to a child with hemophagocytic lymphohistiocytosis and bilateral optic nerve head infiltration: a case report and brief literature review

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a potentially lethal immune system dysregulation in children and adults. Failure to properly inhibit the immune response leads to constant and excessive activity of the cytotoxic T-cells, natural killer (NK) cells, and macrophages. Inflammatory reactions caused by the intense activity of the cellular immune system and cytokine storm in tissues lead to multiple organ failure in this disease. HLH is categorized as primary, which defines as the presence of a predisposing genetic mutation in the immune system, and reactive to an infectious, inflammatory, or malignant trigger. The diagnosis is challenging as it has no clinical or laboratory pathognomonic features. Fever, organomegaly, liver dysfunction, cytopenias, coagulopathy, hemophagocytosis, and neurologic dysfunction are common manifestations of HLH.

Ocular involvement is relatively rare in HLH. Unilateral panuveitis, Purtscher retinopathy, trabecular meshwork involvement, and choroidal infiltration with secondary extension to the retina and optic nerve head (ONH) have been reported previously.

This report aims to introduce a child with HLH and bilateral ONH infiltration.

Case report

A 9-year-old boy, with a history of HLH from 6 months ago, was referred by his pediatric oncologist to the ophthalmic emergency department with a complaint of painless progressive blurred vision in his right eye. On ocular external examination, there was a mild conjunctival injection, chemosis, and proptosis in his right eye (Figure 1). The best-corrected distance visual acuity was 20/40 and 20/20 for his right and left eye respectively. The relative afferent pupillary defect (RAPD) examination was positive for the right eye. Anterior segment examination was unremarkable for both eyes. In the fundus examination, we found an optic disc swelling and peripapillary hemorrhage in the right eye. The left fundus examination showed a mild optic nerve head blurred margin. Regarding the patient's clinical status, differential diagnoses include neoplastic infiltrative optic neuropathy, cytomegalovirus (CMV) optic neuritis, drug toxicity, and CNS involvement with increased intracranial pressure (ICP). For further evaluation, a brain and orbital MRI with gadolinium enhancement (Figure 3), aqueous sampling with a 25-gauge needle for polymerase chain reaction (PCR) to detect CMV, lumbar puncture (LP) to analyze cerebrospinal fluid cytology and biochemistry, and also for ICP measurement, and blood test for hematology and biochemistry were ordered. We summarized the results of the patient's imaging and lab tests in Table 1.

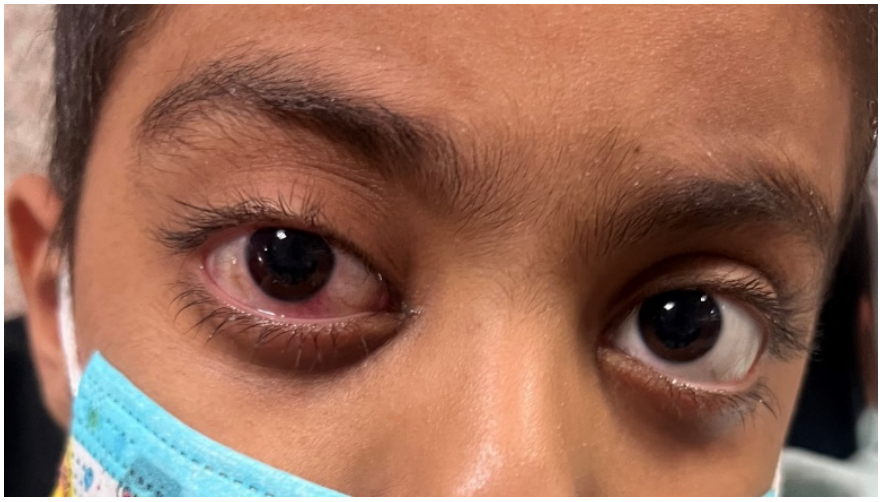

Figure 1- The facial appearance of the patient.

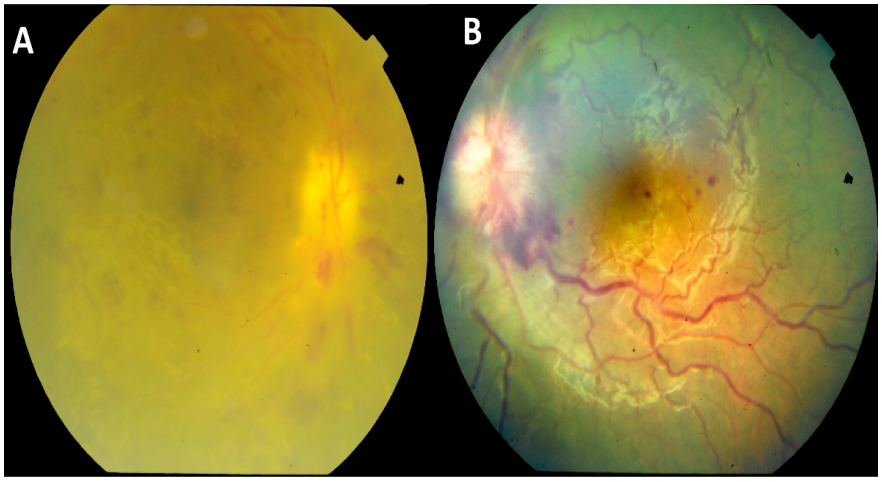

Figure 2- Fundus photograph of the patient: A) Right eye optic disc swelling and epiretinal hemorrhage. B) left eye optic disc swelling and splinter hemorrhage around the disc and macular epiretinal hemorrhage.

After one week, in the first follow-up examination, the optic disc swelling progressed (Figure 2) in both eyes and the visual acuity decreased dramatically to light perception in the right eye and 10/20 in the left eye. The patient was referred to his oncologist to continue systemic chemotherapy and radiotherapy. In the last follow-up visit, the fundus examination revealed disc swelling, retinal edema, and epiretinal hemorrhage in both eyes, and visual acuity deteriorated to no light perception and counting fingers in the right and left eye, respectively. The patient is a candidate for bone marrow transplantation.

Table 2- laboratory test results.

Laboratory test	**result**
Cerebrospinal fluid biochemistry	
Sugar	44 mg/dl
Protein	98.5

Laboratory test	**result**
cholesterol	1 mg/dl
LDH	35 U/L
	CSF analysis: mildly increasing lymphomononuclear cells
Complete blood cell analysis and cell differentiation	
white blood cell	5.4
red blood cell	2.8
hemoglobin	7.2
hematocrit	22
MCV	76
MCH	25
MCHC	32.7
platelet	89
PMN	75
lymphocyte	25
glucose	115 mg/dl
urea	29 mg/dl
creatinine	0.4 mg/dl
AST	32 U/L
ALT	40 U/L
calcium	9.3 mg/dl
sodium	141 meq/l
potassium	3.8
CRP	5 mgr/dl
ESR	55 MM

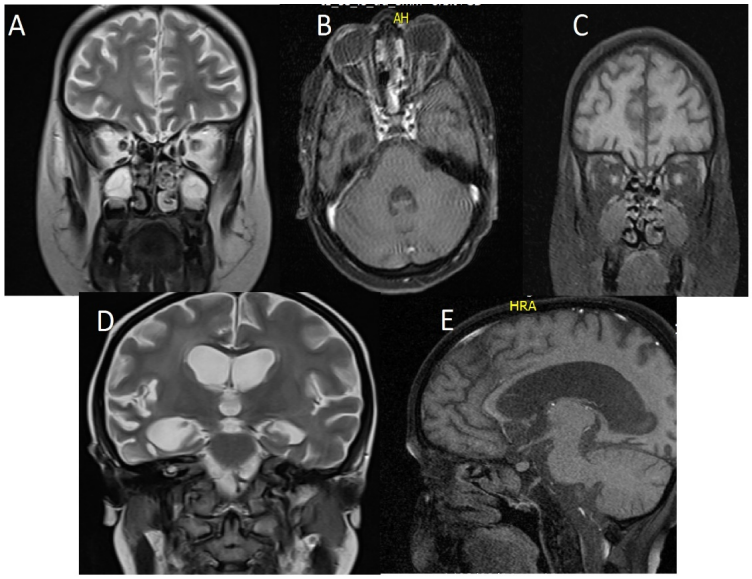

Figure 3- Brain and orbital MRI with and without gadolinium contrast: A) coronal T2 MRI without contrast shows bilateral optic nerve enlargement B) axial T1 MRI with contrast shows bilateral optic nerve enlargement and enhancement C) coronal T1 MRI with contrast shows bilateral optic nerve enlargement

and enhancement D) coronal T2 MRI without contrast shows brain third and lateral ventricles enlargement E) sagittal T1 MRI with contrast shows brain third ventricle enlargement.

Discussion

In this study, we reported a child with HLH presented to us with bilateral painless progressive visual loss. In the ophthalmic examination, we found bilateral optic disc swelling and hemorrhage. HLH is an immune system dysregulation characterized by multiorgan infiltration of macrophages, especially affecting the liver, spleen, lungs, bone marrow, lymph nodes, and kidneys, leading to various signs and symptoms. The mean age of occurrence is 1.8 in children and 50 years old in adults(1).

Ocular involvement is uncommon in HLH. Wang et al., in a study in 2023, showed that old age, autoimmune disorders, and decreasing RBC and platelet counts are independent risk factors of ocular involvement in HLH(2). Retinal hemorrhage, conjunctivitis, corneal infiltration, anterior uveitis, papillitis, and choroidal involvement are the main ophthalmic signs in these patients(2). A literature review regarding ocular involvement in HLH is briefed in Table 2.

Optic nerve head involvement in HLH is rare. A wide range of differential diagnoses should be considered(3). We summarized the clinical approach to our patient in Figure 4. Regarding the patient's immune status, opportunistic infections such as CMV must be investigated and ruled out. Ocular involvement in CMV infection is a serious sight-threatening condition that could be manifested as optic nerve head inflammation(4). The sensitivity and specificity of PCR tests for aqueous samples are 82% and 91%, respectively. The result of the aqueous and blood PCR tests was negative in our patient and we found no evidence of systemic CMV infection. In the brain and orbital MRI, we found bilateral optic nerve infiltration and the CSF analysis showed the brain involvement with tumoral cells. However, ICP was within normal limits. Another differential diagnosis in this patient is an adverse drug complication. There are reports of etoposide-related optic nerve toxicity(5). However, clinical evidence and imaging findings indicate optic neuropathy due to tumoral infiltration, not drug toxicity.

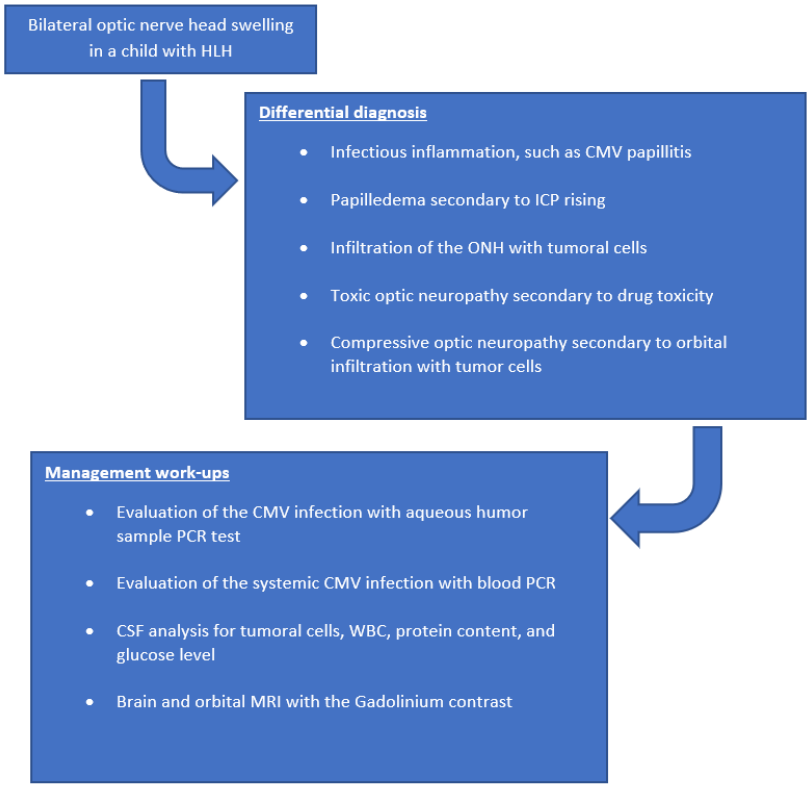

Figure 4- Approach diagram to a patient with HLH and bilateral optic nerve head swelling.

Table 2- Summary of previous studies regarding ocular involvement in HLH.

Study	Year	Type	Main findings
Xu Li et al.(6)	2017	Case report	A 53-year-old man with HLH presented with unilateral panuveitis.
Sebrow et al.(7)	2017	Case report	A 52-year-old woman with HLH presented with the findings of Purts
Suhr et al.(8)	2016	Case report	A 4-week-old neonate with HLH presented with bilateral retinal whi
Wang et al.(2)	2023	Retrospective analysis	Retinal/vitreous hemorrhage is the most common ocular finding in p
Viscaino et al.(9)	2017	Case series	Three cases of adult-onset HLH were reported. Pathologic evaluatio
Engelbert et al.(10)	2007	Case report	A one-month-old female with HLH, presented with bilateral posterio
Chong et al.(11)	2012	Case report	An eight-month-old girl with HLH presented with central nervous sy

Clinical Key points

Infiltrative optic neuropathy in hemophagocytic lymphohistiocytosis is rare but could potentially lead to visual loss. Cytomegalovirus (CMV) optic neuritis, drug toxicity, and CNS involvement with increased intracranial pressure (ICP) are differential diagnoses that have to be considered.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Consent for publication was acquired from the legal guardian of the patient.

Availability of data and materials: The datasets used during the current study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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