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Cytotoxic Lesion of the Corpus Callosum (CLOCC) + Hemophagocytic Lymphohistiocytosis (HLH): The Deadly NEURO-IMMNUNE DUO: A Case Report

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome caused by uncontrolled activation of macrophages and cytotoxic lymphocytes. Neurological involvement occurs in 30–70% of patients; however, isolated cytotoxic lesions of the corpus callosum (CLOCC) are uncommon and may mimic infectious encephalitis. We report an 11-year-old previously healthy boy who presented with fever and headache for four days followed by vomiting, altered sensorium, and slurred speech for two days. On admission, his Glasgow Coma Scale was E4V4M6 (14/15). Magnetic resonance imaging of the brain demonstrated diffusion restriction involving the splenium of the corpus callosum with corresponding T2/FLAIR hyperintensity, consistent with CLOCC. Cerebrospinal fluid examination showed 2 lymphocytes/mm³, protein 39.1 mg/dL, glucose 49.5 mg/dL, and 4–6 red blood cells/high-power field. CSF Bio Fire multiplex PCR and extensive infectious investigations were negative. Laboratory evaluation revealed bicytopenia, serum ferritin 65,000 ng/mL, lactate dehydrogenase 2360 U/L, D-dimer 9338 ng/mL, hypertriglyceridemia, hypofibrinogenemia (228 mg/dL), transaminitis, and elevated inflammatory markers. The patient fulfilled HLH-2004 diagnostic criteria for secondary HLH and was treated with broad-spectrum antimicrobials, intravenous acyclovir, intravenous immunoglobulin, pulse methylprednisolone followed by oral prednisolone, resulting in progressive neurological recovery and normalization of inflammatory markers. This case highlights CLOCC as a rare early neuroimaging manifestation of HLH-associated cytokine storm. In children presenting with acute encephalopathy, persistent fever, and isolated splenial lesions despite normal cerebrospinal fluid and negative infectious studies, HLH should be considered to facilitate timely immunomodulatory therapy and improve neurological outcomes.

Keywords: Hemophagocytic lymphohistiocytosis; Cytotoxic lesion of the corpus callosum (CLOCC); Mild encephalitis/encephalopathy with reversible splenial lesion (MERS); Secondary HLH; Hyperferritinemia; Paediatric encephalopathy

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome caused by uncontrolled activation of macrophages, cytotoxic T lymphocytes, and impaired natural killer cell function, resulting in excessive cytokine release and multiorgan dysfunction. It is classified as primary (familial) or secondary (acquired), with infections being the most common trigger in children. Persistent immune activation leads to a cytokine storm, causing prolonged fever, hepatosplenomegaly, cytopenias, liver dysfunction, coagulopathy, Hyperferritinemia, hypertriglyceridemia, and progressive organ failure. Because its clinical presentation often mimics severe sepsis and other inflammatory disorders, early diagnosis using the HLH-2004 criteria is crucial to improve survival.

Central nervous system involvement occurs in up to 70% of paediatric patients and is associated with increased morbidity and mortality. Neurological manifestations include altered sensorium, seizures, focal deficits, and encephalopathy, while neuroimaging findings are variable. Cytotoxic lesions of the corpus callosum (CLOCC) are transient magnetic resonance imaging abnormalities characterized by restricted diffusion within the splenium of the corpus callosum and are believed to result from cytokine-mediated cytotoxic oedema. Although reported with infections, autoimmune diseases, and metabolic disorders, CLOCC as the presenting manifestation of secondary HLH is rare.

Case Report

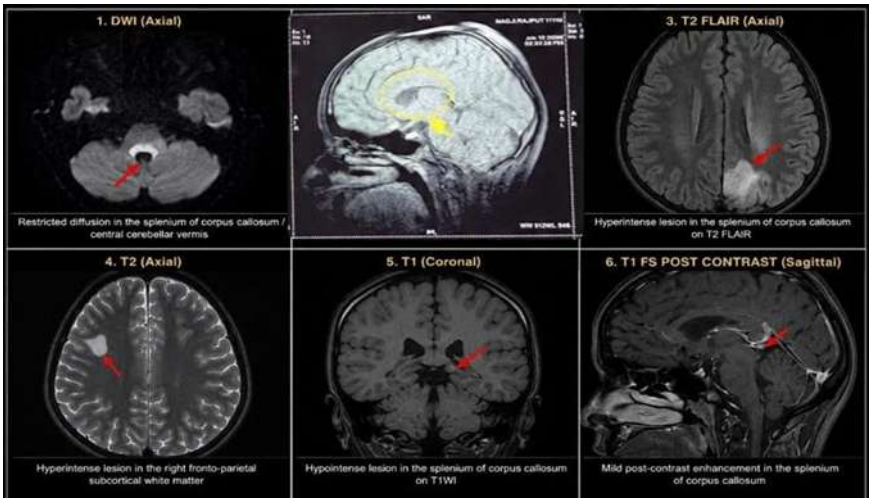
An 11-year-old previously healthy boy transferred from other hospital presented with high-grade fever and generalized headache for four days, followed by repeated vomiting, altered sensorium, and slurred speech for two days. There was no history of seizures, trauma, recent vaccination, tuberculosis contact, rash, neck stiffness, animal bite, or toxin exposure.

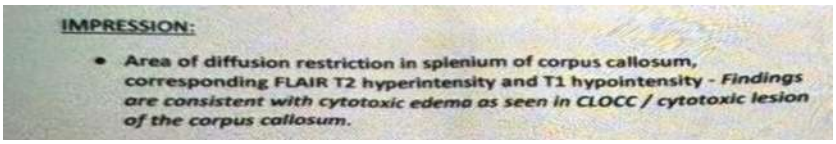
Clinical Examination

On admission, the child was febrile with a Glasgow Coma Scale (GCS) score of E4V4M6 (14/15). Neurological examination revealed altered sensorium without focal neurological deficits or meningeal signs. Abdominal examination revealed significantly enlarged liver span around 12cm and palpable of 2-3cm. Examination of the cardiovascular, respiratory was otherwise unremarkable.

Neuroimaging Findings

Pt came with outside Magnetic resonance imaging (MRI) of the brain reports which demonstrated a well-defined lesion involving the splenium of the corpus callosum, showing restricted diffusion on diffusion-weighted imaging with corresponding low apparent diffusion coefficient (ADC) values, T2/FLAIR hyperintensity, and T1 hypo intensity, consistent with a cytotoxic lesion of the corpus callosum (CLOCC).





Laboratory Investigations

Outside Cerebrospinal fluid (CSF) examination revealed clear, colourless fluid with protein 39.1 mg/dL, glucose 49.5 mg/dL, two lymphocytes/mm³, no neutrophils, and 4–6 red blood cells/high-power field. CSF Bio Fire multiplex polymerase chain reaction panel was negative. Initial infectious workup, including Malaria antigen, Extended Widal test, Leptospira serology, Dengue antigen and Blood cultures were negative. Laboratory investigations demonstrated Bicytopenia (Total cell count: 0.5* 1000cells/cumm and Platelets: 90000), markedly

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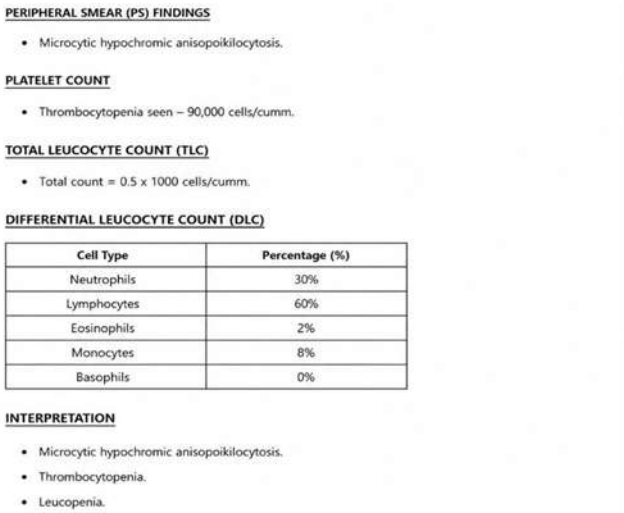
elevated serum ferritin (65,000 ng/mL), lactate dehydrogenase (2360 U/L), D-dimer (9338 ng/mL), hypertriglyceridemia (221mg/dl), hypofibrinogenemia (228 mg/dL), elevated liver transaminases (SGOT: 967, SGPT: 262) and raised inflammatory markers (CRP: 132). Based on the HLH-2004 diagnostic criteria, a diagnosis of secondary hemophagocytic lymphohistiocytosis (HLH) was established.



PERIPHERAL SMEAR (PS) FINDINGS

- Microcytic hypochromic anisopoikilocytosis.

PLATELET COUNT

- Thrombocytopenia seen – 90,000 cells/cumm.

TOTAL LEUCOCYTE COUNT (TLC)

- Total count = 0.5 x 1000 cells/cumm.

DIFFERENTIAL LEUCOCYTE COUNT (DLC)

Cell Type	Percentage (%)
Neutrophils	30%
Lymphocytes	60%
Eosinophils	2%
Monocytes	8%
Basophils	0%

INTERPRETATION

- Microcytic hypochromic anisopoikilocytosis.
- Thrombocytopenia.
- Leucopenia.

Treatment And Clinical Outcome

Empirical therapy with intravenous Gentamycin, Ceftriaxone, Vancomycin, Acyclovir, Fluconazole and supportive intensive care was initiated while infectious causes were being evaluated. Following confirmation of HLH, the child received Intravenous Immunoglobulin (IVIG) 1g/kg/dose for 2 days and Methylprednisolone Pulse Therapy was started at 30mg/kg/day, followed by tapering of intravenous methylprednisolone to 2mg/kg/day over 10 days and switching to oral prednisolone. The patient demonstrated progressive improvement in sensorium and neurological function, with a corresponding decline in inflammatory markers. He was discharged neurologically intact with complete clinical recovery.

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome caused by uncontrolled activation of macrophages and cytotoxic lymphocytes, leading to excessive cytokine release and multiorgan dysfunction. Neurological involvement occurs in approximately 30–70% of pediatric patients and often mimics acute infectious encephalitis, making early diagnosis challenging. Our patient initially presented with fever, headache, vomiting, altered sensorium, and dysarthria, all of which are classical features of encephalitis. However, subsequent clinical, laboratory, and radiological findings favored secondary HLH with central nervous system (CNS) involvement.

The major diagnostic challenge was differentiating HLH-associated neuroinflammation from infectious encephalitis. Although both conditions present with fever and altered mental status, encephalitis is typically associated with cerebrospinal fluid (CSF) pleocytosis, pathogen detection, and characteristic cortical or temporal lobe involvement on neuroimaging. In contrast, our patient had normal CSF findings with a negative CSF Bio Fire panel, arguing against an infectious etiology. Instead, the presence of persistent fever, bicytopenia, markedly elevated ferritin, hypertriglyceridemia, hypofibrinogenemia, and bone marrow hemophagocytosis fulfilled the diagnostic criteria for HLH.

The markedly elevated inflammatory biomarkers further supported the diagnosis. Serum LDH (2360 U/L) reflected extensive tissue injury secondary to cytokine-mediated inflammation, while a markedly elevated D-dimer (9338 ng/mL) indicated activation of coagulation and fibrinolysis, both recognized markers of severe disease and poor prognosis in HLH. Such profound elevations are uncommon in uncomplicated viral encephalitis and should prompt evaluation for hyperinflammatory syndromes.

Magnetic resonance imaging demonstrated a cytotoxic lesion of the corpus callosum (CLOCC), a rare but

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increasingly recognized manifestation of systemic inflammatory disorders. CLOCCs are believed to result from cytokine-mediated glutamate excitotoxicity, intramyelinic edema, and transient cytotoxic edema, particularly affecting the splenium of the corpus callosum. Although described in viral infections, autoimmune diseases, epilepsy, and multisystem inflammatory syndrome in children, CLOCC has rarely been reported in HLH. Recognition of this reversible imaging pattern in the appropriate clinical setting should raise suspicion for cytokine-mediated neuroinflammation rather than primary infectious encephalitis.

The patient's rapid neurological improvement following pulse methylprednisolone strongly supported an inflammatory rather than infectious process. Unlike infectious encephalitis, which primarily requires antimicrobial therapy, HLH necessitates prompt immunosuppressive treatment to halt the cytokine storm and prevent irreversible neurological injury and multiorgan failure.

This case highlights the importance of considering HLH in children presenting with an encephalitis-like illness accompanied by persistent fever, cytopenias, Hyperferritinemia, elevated LDH and D-dimer, and negative infectious investigations. Early application of HLH diagnostic criteria, recognition of CLOCC as a marker of cytokine-mediated CNS involvement, and timely initiation of immunomodulatory therapy are crucial for improving neurological outcomes and survival.

Conclusion

This case underscores the diagnostic challenge posed by hemophagocytic lymphohistiocytosis (HLH) presenting as acute encephalitis with isolated neurological manifestations. In children with persistent fever, encephalopathy, cytopenias, Hyperferritinemia, and negative infectious work-up, HLH should be considered early to avoid delays in life-saving immunomodulatory therapy. The presence of a cytotoxic lesion of the corpus callosum (CLOCC) may serve as an important radiological clue to cytokine-mediated neuroinflammation. Prompt recognition, systematic evaluation using HLH diagnostic criteria, and early corticosteroid therapy can result in complete neurological recovery and significantly improve survival.

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