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# Central nervous system imaging findings of hemophagocytic syndrome☆

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ABSTRACT

We present a rare case of intracranial involvement in hemophagocytic lymphohistiocytosis (HLH) in an adult patient. MRI features in HLH may mimic those of other neoplastic, infectious, or inflammatory disorders. Key imaging findings correlate to central nervous system inflammation and include diffuse leptomeningeal enhancement, white matter changes with variable enhancement, hemorrhage, and restricted diffusion. Recognition of the imaging characteristic in correlation with clinical presentation, laboratory values, and biopsy findings is essential for making a correct diagnosis.



## 1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome characterized by diffuse infiltration of activated lymphocytes and macrophages involving multiple organs, including the central nervous system (CNS). HLH is typically related to inherited immune deficiencies or viral infections in children and young adults. In adults, it can be related to malignancy, particularly lymphoma [1,2]. Protean imaging features of HLH overlap with other inflammatory, infectious, and neoplastic disorders. Therefore, imaging findings need to be correlated with suspicious clinical and laboratory abnormalities such as fever, hepatosplenomegaly, neurologic symptoms, rash, pancytopenia, hypertriglyceridemia, hyperferritinemia, and hypofibrinogenemia [3,4]. In addition, correlation with bone marrow, spleen, lymph node, or other solid organ biopsy showing hemophagocytosis can aid in diagnosis.

Previous case reports have described imaging findings of CNS involvement; however, these cases have been predominantly of children [5,6]. We present a rare case of an adult patient with a clinical and radiological diagnosis of HLH with CNS involvement. Since the imaging features in the CNS are not specific to HLH, knowledge of the imaging findings, in combination with other clinical and laboratory information, is helpful to achieve a correct diagnosis and expedite treatment.

## 2. Case report

A 56-year-old, previously healthy female developed weight loss, fatigue, fevers, and night sweats. She was evaluated by her local oncologist, and no etiology was identified. She continued to decline clinically, developing profound generalized weakness and encephalopathy. After extensive outside workup including comprehensive blood laboratory analysis and infectious disease testing, computed tomographic (CT) scans of the chest, abdomen, and pelvis, bone marrow biopsy, esophagogastroduodenoscopy and colonoscopy with biopsies, liver biopsy, paracentesis, mammogram, and abdominal ultrasound without determination of an underlying cause, she was referred to our institution for further evaluation.

Laboratory studies revealed severe anemia and other cytopenias, monocytosis, and elevated liver enzymes. Cytology from paracentesis showed erythrophagocytosis, making HLH a diagnostic consideration. Additional laboratory studies showed markedly elevated ferritin and soluble interleukin-2 receptor levels, compatible with HLH. Prior liver and bone marrow biopsy samples were reevaluated, and hemophagocytosis was present, leading to a clinical diagnosis of HLH.

The patient's mental status continued to decline, despite adjustment of her pain and sedative medications. A brain magnetic resonance imaging (MRI) was ordered to evaluate for any underlying etiology. This initial brain MRI demonstrated diffuse, profound leptomeningeal and mild pachymeningeal enhancement (Fig. 1), abnormalities consistent with CNS involvement by an inflammatory process such as HLH. The patient was started on aggressive treatment with chemotherapy and high-dose corticosteroids. She initially improved, and chemotherapy was discontinued after 4 months. Unfortunately, she was readmitted 2 weeks later for increasing weakness and stroke symptoms.

Repeat MRI upon readmission (at a 3-month interval from the initial images) demonstrated progression of brain abnormalities with the development of innumerable nonenhancing new foci of T2 hyperintensity

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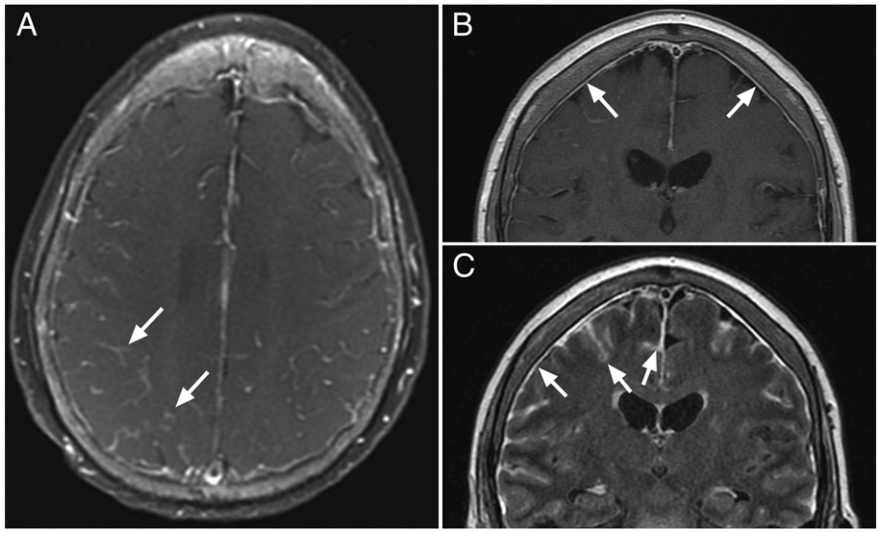


**Fig. 1.** Axial spin echo T1-weighted with fat saturation (repetition time [TR] 650/echo time [TE] 20) (A), coronal spin echo T1-weighted (TR416/TE13) (B), and T2W-FLAIR (TR11002/TE149) (C) postgadolinium images from the initial brain MRI demonstrate profound diffuse leptomeningeal (A, C) and mild pachymeningeal (B, C) enhancement (examples at arrows).

scattered within the supratentorial white matter (Fig. 2A). Some of these foci demonstrated restricted diffusion with low signal on the apparent diffusion coefficient (ADC) maps (Fig. 2B and C). The abnormal lepto- and pachymeningeal enhancement observed in the initial MRI had nearly completely resolved, however (Fig. 3). Lumbar puncture was also performed (4 months after initial evaluation). Cerebrospinal fluid (CSF) testing included opening pressure, protein, glucose, cell count, oligoclonal bands, synthesis rate, and IgG index. Cultures for bacterial, viral, fungal, and other infectious agents were negative. Cytology revealed no malignant cells. The only abnormality found was mildly elevated total protein at 40 mg/dl (normal 0–35 mg/dl). The patient was treated for recurrent, progressive HLH. Clinical improvement was again observed.

Two months later, with worsening clinical status, a third brain MRI was obtained. This MRI showed marked interval enlargement of the numerous T2 hyperintense areas within the bihemispheric white matter and basal ganglia, many of which had restricted diffusion and gadolinium enhancement (Fig. 4). A few of the T2 hyperintense lesions also demonstrated hypointensity on gradient echo sequences, suggestive of hemorrhage (Fig. 5). These imaging features were compatible with inflammatory meningitis and diffuse cerebritis secondary to intracranial HLH and correlated with the patient's worsening clinical picture.

Chemotherapy was subsequently discontinued due to renal failure and profound cytopenias. She subsequently developed polymicrobial bacteremia and died 6 months after the initial diagnosis.

## 3. Discussion

HLH is a hyperinflammatory syndrome with uncontrolled proliferation of activated, nonneoplastic lymphocytes and macrophages, resulting in phagocytosis of other blood cells and overproduction of inflammatory cytokines [2,4]. Clinically, HLH is subdivided into primary and secondary subsets. Primary cases are related to genetic abnormalities and are usually diagnosed in first 2 years of life [4]. Secondary cases have been linked with acquired viral infections, malignancies, prolonged intravenous nutrition, organ/bone marrow transplantation, and autoimmune disorders [4]. Viral-associated HLH has a lower mortality than other etiologies [3]. An underlying process is not always elucidated, and mortality is high. Treatment often consists of high-dose steroids, chemotherapy, antimicrobials, and intravenous immune

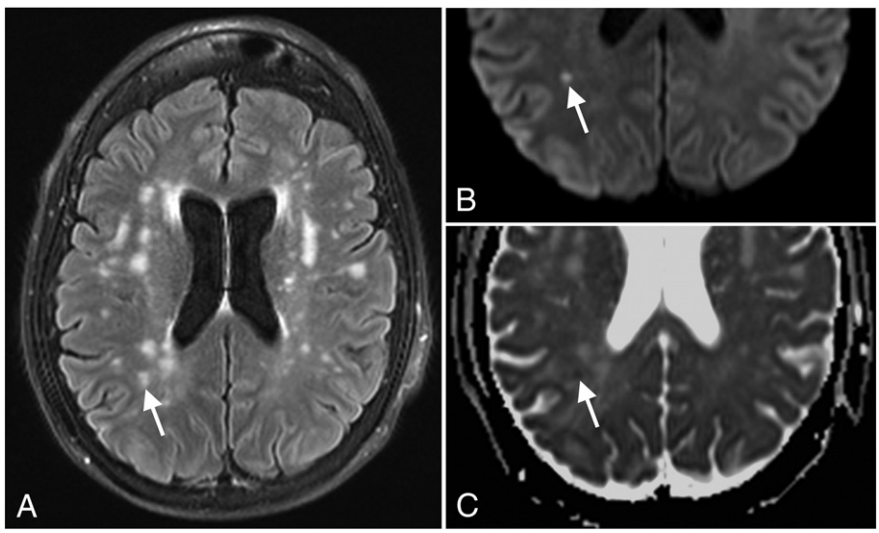


**Fig. 2.** Follow-up MRI 3 months later demonstrates development of innumerable new foci of T2 hyperintensity scattered within the supratentorial white matter (A, axial T2 FLAIR with fat saturation (TR 9000/TE 139)), several of which had restricted diffusion (B, DWI (TR7500/TE78)) with correlative low ADC (C, axial ADC) shown by the arrows.