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An Elusive Seizure

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Abstract

We present a case of a healthy 62-year-old woman who developed recurrent seizures preceded by subacute cognitive slowing, ataxia, night sweats, and weight loss. She was found to have cytopenias, multifocal T2/FLAIR hyperintensities on magnetic resonance imaging (MRI), and magnetic susceptibility artifact lesions on susceptibility weighted imaging (SWI). Her symptoms, imaging and laboratory abnormalities all improved with high-doses of steroids and intravenous immunoglobulin (IVIG). But recurred several weeks after completing treatment. Despite extensive work-up, she required multiple hospitalizations and repeat diagnostic studies to arrive at a diagnosis. With an expert discussant in hematology and oncology, we review the differential diagnosis and stepwise approach of unexplained neuro-inflammatory syndromes with cytopenias and systemic symptoms. Our case highlights how time, empiric treatment response, and repeated diagnostic studies refine differential diagnoses and subsequent evaluation. After revealing the diagnosis, we discuss the heterogenous clinical manifestations of this disease process.

Keywords

hemophagocytic lymphohistiocytosis, cytopenia, cerebral microhemorrhages, seizure, clinical reasoning, hematology

Case Presentation and Expert Discussant

A healthy 62-year-old saleswoman was admitted with 3 episodes of whole-body rhythmic shaking and abnormal facial movements lasting 1 minute each. In the preceding weeks, she had left-sided weakness, clumsiness, inattention, slowed ambulation, night sweats, fatigue, and 14-lb unintentional weight loss. She denied recent illness, fevers, headaches, and neck pain. There was no history of seizures, head trauma, new medications, tobacco, alcohol, or drug use. Family history was non-contributory. On admission, the patient was afebrile, blood pressure 110/62, heart rate 87, with oxygen saturation 97% on 2 L/min. She was obtunded, unresponsive to noxious stimuli, and did not follow commands. Neurologic exam revealed 3+ reflexes throughout. The patient received a 1-gram load of levetiracetam yet remained obtunded for > 3 hours after her seizure.

Gerald Hsu, MD PhD (Hematology/Oncology): The description of left-sided weakness prior to seizures suggests a central nervous system (CNS) process involving the right hemisphere. Meningeal infection is less likely in the absence of fever, headache or neck pain, although parchenymal infections remain a possibility. Drug use, medications, and trauma are also unlikely. Vascular etiologies (i.e. stroke, vasculitis, cerebral venous sinus thrombosis), solid or hematologic malignancy like lymphoma could explain the patient's neurologic deficits and seemingly unprovoked seizure. The presence of B-symptoms, night sweats and >10% weight loss over 6 months, may be observed with cancers and inflammatory conditions, so MRI of the brain should be performed. A prolonged post-ictal state raises the possibility of ongoing seizures. Electroencephalography (EEG) and lumbar puncture (LP) should be obtained.

Laboratory studies revealed pancytopenia, elevated lactate, normal liver function tests, unremarkable urinalysis, negative HIV antibody, and negative urine toxicology screen (Table 1). MRI brain revealed abnormal foci of gadolinium enhancement in the right posterior frontal lobe, right corona radiata, and left body of the corpus callosum within areas of T2/FLAIR hyperintensity (Figure 1). These multifocal areas were associated with

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Table 1. Notable Clinical Laboratory Results.

Variable	First admission	3 months after first admission	Fourth admission	Reference range
Complete Blood Count				3,500-12,500/uL
White blood cell Count	0.9	4.5	6.2	12.0-15.5 g/dL
Hemoglobin	10.0	13.8	9.3	140K-400K/uL
Platelets	65,000	196,000	38,000	1500-8000/uL
Absolute Neutrophil Count	100	2700	5500	
Serum Studies				0.7-1.9 mmol/L
Lactate	12.0		2.0	22-30 mEq/L
Bicarbonate	13.0		25	≤ 0.5 mg/dL
C-reactive protein (CRP)	8.6			0-30mm/hr
Erythrocyte sedimentation	19			
Rate (ESR)	Negative			
HIV Ag/Ab				
Urine Studies				
Urinalysis	Unremarkable			
Toxicology Screen*	Negative			
Serologic Rheumatologic Work-up				0-52 U/L
Angiotensin converting enzyme (ACE)	95			0-13.9 IU/ml
Rheumatoid Factor	<10			
Anti-neutrophil cytoplasmic antibody	Negative			
Anti-dsDNA	Negative			
Anti-Ro/SSA	Negative			
Anti-La/SSB	Negative			
Anti-centromere	Negative			
Anti-Scl70	Negative			

*Toxiciology screen includes: amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, and cannabinoids.

magnetic susceptibility artifact lesions due to microhemorrhages on SWI (Figure 2A). EEG demonstrated periodic right temporal slowing without epileptiform activity. Cerebrospinal fluid (CSF) analysis revealed 2 unique oligoclonal bands (OCBs), but normal WBC, protein, glucose, and negative venereal disease research laboratory testing. CSF herpes simplex virus polymerase chain reaction, blood, urine, and CSF bacterial cultures returned negative and empiric IV acyclovir, vancomycin, and ceftriaxone were discontinued. The patient's mental status returned to baseline within 24 hours, but left-sided weakness and fatigue persisted.

New pancytopenia warrants peripheral blood smear review and evaluation for hypo-proliferative, hyper-proliferative, and hemolytic anemias. In the absence of a microangiopathic hemolytic anemia, bone marrow biopsy (BMBx) is warranted. The serum lactate elevation is likely secondary to the patient's seizure. There are several broad categories that may account for multifocal brain lesions and OCBs—autoimmune including paraneoplastic phenomena, infectious, inherited, demyelinating, granulomatous, and malignant processes—but few diagnoses would unify the imaging findings, systemic symptoms and pancytopenia. Before obtaining labs to evaluate for these diagnoses (eg. paraneoplastic antibody panel, antinuclear antibody, anti-double-stranded DNA (anti-dsDNA), complement levels, or anti-HTLV-1), evaluation of pancytopenia should be pursued.

Her CRP was 8.6 (ref range <=0.5 mg/dL), ESR 19 (Ref: 0-30mm/hr), and ferritin 1951 (Ref: 22-291 ng/mL). Coagulation profile was within normal limits and peripheral blood smear was unremarkable without schistocytes or spherocytes. No malignant cells were identified on CSF cytologic analysis and CSF flow cytometry showed no evidence of a B-cell or T-cell lymphoproliferative disorder. CSF autoimmune and paraneoplastic encephalitis antibody testing was negative. CT chest, abdomen, and pelvis with contrast and mammography were unrevealing. Due to concern for a paraneoplastic process, Positron Emission Tomography (PET)/CT was performed to evaluate for occult malignancy. Imaging revealed moderate fluorodeoxyglucose (FDG) uptake in the bone marrow concerning for a marrow replacement process and a linear focus of moderate FDG uptake in the left proximal humerus without a corresponding anatomic abnormality. BMBx demonstrated 70% marrow cellularity with 10% monocytes on flow cytometry and <5% blasts. Workup for rheumatologic causes revealed an elevated angiotensin converting enzyme (ACE) level (Table 1). Given residual concern for a paraneoplastic process and no clear site for tissue biopsy, the patient was empirically treated with IVIG and pulse dose methylprednisolone. Her fatigue, left-sided weakness, and pancytopenia improved with treatment. MRI Brain 3 months post-discharge revealed decreased T2/FLAIR abnormalities.

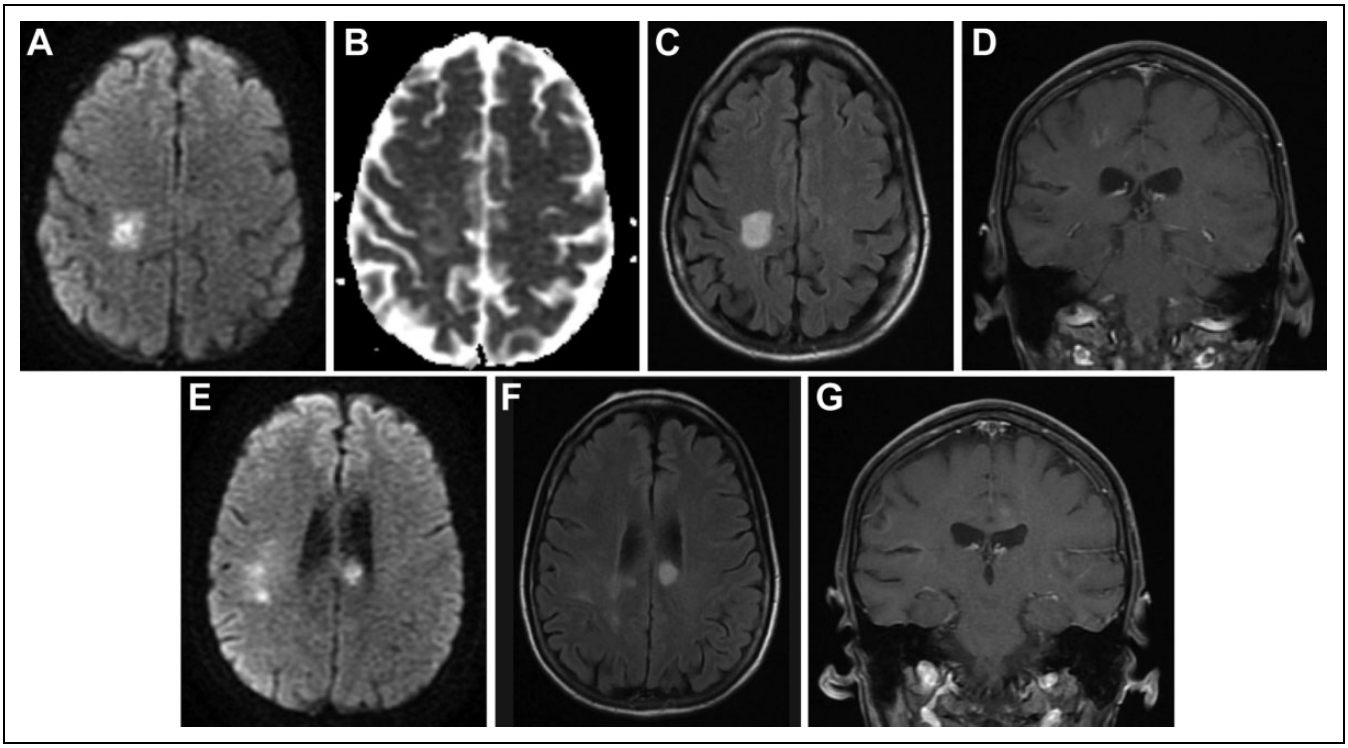

Figure 1. MRI Brain showing progression of disease from initial presentation. (A) Axial DWI, (B) corresponding axial ADC, and (C) axial T2 FLAIR images highlighting lesion within the right corona radiata taken from patient's initial hospital admission. (D) Coronal T1 post-gadolinium contrast image demonstrating wispy enhancement within the inferior aspect of this lesion. (E) Axial DWI and (F) axial T2 FLAIR images from more inferior location demonstrating patchy lesions involving left corpus callosum and right juxtacortical white matter; of note, DWI changes were largely T2 shine-through for these lesions and so ADC is not presented here. (G) Coronal T1 post-gadolinium contrast image demonstrating faint enhancement within left corpus callosum lesion.

Elevated ferritin is a non-specific finding and can be seen in a variety of inflammatory conditions in adults.[1,2] However, in the setting of acute critical illness with cytopenias, hyperferritinemia to this degree warrants consideration of hemophagocytosis (HPC) due to acute infection, HIV, malignancy, hemophagocytic lymphohistiocytosis (HLH), or macrophage activation syndrome. The patient's presentation with seizure and sudden cytopenias suggests HLH, but is less likely in the absence of fever and hepatitis. The absence of HPC on BMBx neither supports nor excludes HLH. Monocytosis in the bone marrow may be due to primary processes such as chronic myelomonocytic leukemia or reactive to high cellular turnover, HLH, or granulomatous. Based on the evaluation to date, steroids would be an appropriate component of therapy for many of the suspected diagnoses: HLH, systemic lupus erythematosus (SLE), sarcoidosis, or paraneoplastic conditions. The duration of response and the evolution of symptoms will guide subsequent evaluations and interventions.

Over the next year, the patient had 2 additional hospitalizations for recurrent seizures despite therapeutic anti-epileptic drug (AED) levels, preceded by prodromal symptoms (cognitive slowing, ataxia, night sweats, and fatigue). On each admission, the patient had re-emergence of pancytopenia and T2/FLAIR hyperintensities on MRI Brain. Repeat CT demonstrated new 15 cm splenomegaly. Repeat LP revealed 3+ unique OCBs. Repeat CSF and serum paraneoplastic panels were negative. The patient was again treated with IVIG and prolonged steroid courses with symptom resolution, a normalized CBC, and improvement in white matter hyperintensities.

Two features standout to date: chronicity and steroid-responsiveness. The relapsing and remitting symptoms, pancytopenia, and MRI findings are not typical presentations of HLH or untreated malignancy. Paraneoplastic syndromes with neurologic manifestations can precede a cancer diagnosis by years and the absence of an identified paraneoplastic antibody does not exclude it. An atypical presentation of HLH with an indolent course is also a rare possibility, as seen in a variant of familial HLH. The resolution of symptoms, laboratory, and imaging abnormalities with steroids and/or IVIG suggest an autoimmune etiology, such as SLE, sarcoidosis, or a lymphoproliferative disorder. All of these conditions can be associated with pancytopenia. The unremarkable serologic testing to date and elevated ACE level makes sarcoidosis a likely diagnosis. To further evaluate neurologic sarcoidosis with hematologic manifestations,

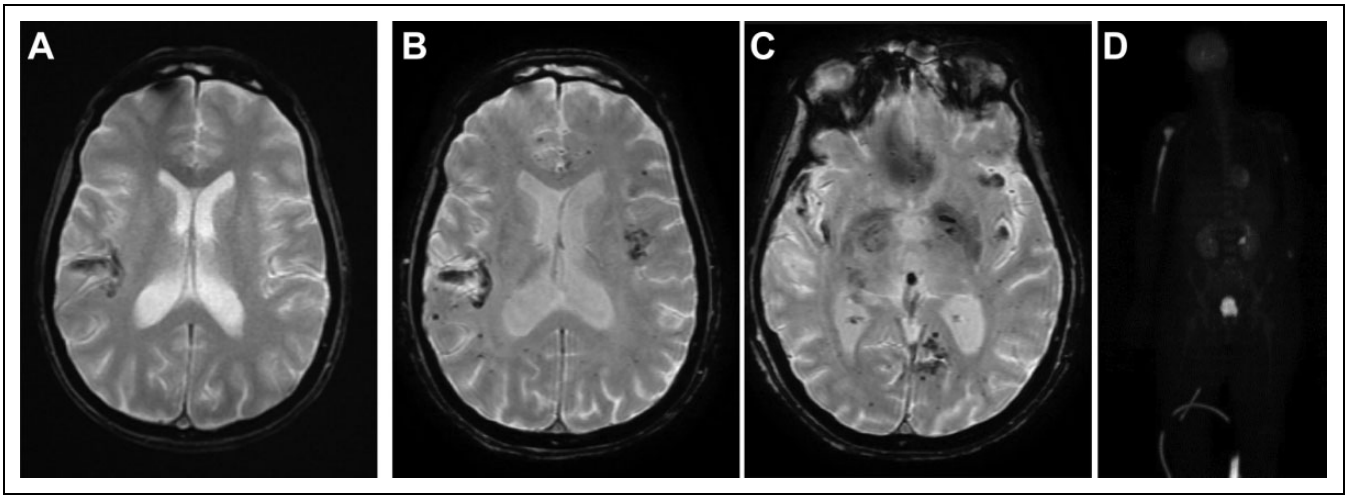

Figure 2. MRI Brain showing progressive microhemorrhages over course of illness and PET imaging revealing systemic imaging findings. (A) Axial susceptibility-weighted image demonstrating multifocal susceptibility artifact especially involving right parietal cortex at initial presentation. (B) Axial susceptibility-weighted image at corresponding level and (C) more inferior level taken from patient's fourth hospital admission demonstrating progressive microhemorrhages over the course of illness. (D) Whole-body PET scan during the fourth admission revealing diffuse R humeral FDG avidity and focal avidity in L humeral diaphysis.

tissue examination for granuloma formation is warranted. Due to the challenge and morbidity of obtaining neural tissue, identifying potential extraneural sites of involvement and re-reviewing BMBx should be done.

Fourteen months after initial presentation, the patient developed acute-onset L-sided arm shaking, dysarthria, facial droop, and subsequent unresponsiveness. One week prior, she developed shuffling gait, night sweats, irritability, and intermittent fevers. Admission vitals were: temperature 39.2C, heart rate 124, blood pressure 124/53, respiratory rate 24, and oxygen saturation of 84% on room air that rose to 100% with facemask. Repeat CBC revealed anemia and thrombocytopenia (Table 1). Lumbar puncture demonstrated an elevated CSF protein to 116 mg/dL (Ref 15-50 mg/dL), but did not reveal pleocytosis. Repeat CSF cytology and flow cytometry were negative for malignant cells. Ferritin was elevated at 3937 ug/L. CT revealed unchanged splenomegaly. MRI brain demonstrated extensive confluent FLAIR white matter hyper-intensities in the right insula extending to the right superior gyrus and multifocal areas of susceptibility artifact consistent with microhemorrhages (Figure 2B-C). MRA demonstrated diffuse progressive vasculopathy with beading/irregularity and diminutive caliber. A formal cerebral angiogram performed 1 month prior to current admission was normal, suggesting that the vascular changes fluctuated in intensity (angiogram done after 3 weeks of stopping all steroids). Despite multiple AEDs, the patient had breakthrough seizures and she was sedated with propofol with seizure abatement. She developed intermittent hypotension down to 80s/40 s requiring norepinephrine.

Symptom relapse invites another opportunity to reassess diagnoses. The neurologic symptoms are again accompanied by anemia, thrombocytopenia, elevated ferritin, but now include fever, hypotension, and hypoxia. Prior blood smears have not revealed schistocytes or spherocytes, but their absence does not rule out a hemolytic anemia. With concurrent thrombocytopenia and neurologic findings, TTP with reversible posterior leukoencephalopathy syndrome (RPLS) should be considered. However, TTP associated with pulmonary involvement is rare and does not account for hypotension. The patchy, asymmetric white matter is also not consistent with typical radiographic findings with RPLS. HLH with CNS involvement could account for all of the clinical features and evaluation of other HLH diagnostic criteria should be pursued if laboratory evaluation reveals no evidence of hemolytic anemia. Other diagnoses on the differential include those that are consistent with the new MRA findings of diffuse progressive vasculopathy, including small-vessel vasculitides, cerebral amyloidosis, neurosarcoidosis, and primary CNS angiitis. However, the lack of CSF pleocytosis argues against these entities, nor would these diagnoses account for all features of this patient's presentation.

Peripheral smear and hemolysis workup were unrevealing. Laboratory studies evaluating for HLH are listed in Table 2. PET scan demonstrated diffuse R humeral FDG avidity and focal L humeral diaphysis FDG uptake without corresponding anatomic abnormality (Figure 1E). Right humerus MRI revealed extensive bone marrow replacement with T2 hyperintensity. Random skin biopsies were negative for intravascular lymphoma. Due to the location of the white matter hyper-intensities close to the motor cortex, brain biopsy was not performed. Right humeral neck BMBx at the area of FDG avidity and marrow replacement demonstrated large lymphoid cells that were strongly positive for tumor markers consistent with diffuse large B-cell lymphoma (DLBCL).

Table 2. Clinical Criteria for Hemophagocytic Lymphohistiocytosis.*

Criteria	Patient findings during fourth admission	Reference Range
Fever	Present	
Splenomegaly	Present	
Cytopenia in at least 2 of 3 cell lines	Present	
Hypertriglyceridemia and/or hypofibrinogenemia		
Fasting triglycerides ≥ 265 mg/dL	323 mg/dL	≤ 200 mg/dL
Fibrinogen ≤ 150 mg/dL		
Low or absent NK-cell activity	>500 LU30	7-25 LU30
Ferritin ≥ 500 ug/L	3937	22-291 ug/L
Soluble Interleukin-2 receptor (sIL-2 R) ≥ 2400 U/mL	11,040	≤ 1033 U/mL
Hemophagocytosis in bone marrow, spleen, or lymph node	Not observed	

*Diagnosis of HLH requires either a molecular diagnosis consistent with HLH or fulfilling 5 of the 8 clinical criteria from above.

This patient now has a diagnosis of DLBCL of the right humerus. In the absence of documented lymphoma in lymph nodes, brain, or extranodal sites, then this represents a rare lymphoma subtype, primary Non-Hodgkin's Lymphoma (NHL) of bone. The severity of the systemic inflammatory response in this patient suggests an alternate or overlaid etiology. The constellation of hypotension, respiratory failure, cytopenias, extremely elevated ferritin and sIL-2, and splenomegaly strongly suggest a concurrent diagnosis of HLH. Most adult cases of HLH are in response to an infection, autoimmune causes, or malignancy. In this case, the patient's HLH is likely secondary to NHL.

Her steroid-responsive neurologic symptoms and neuroimaging lesions can be manifestations of CNS-related complications of HLH (CNS-HLH). Alternatively, they could be due to CNS involvement of her NHL, including secondary CNS lymphoma or intracerebral, intravascular lymphoma. For all 3 entities, definitive diagnosis requires histologic confirmation. Unfortunately, this patient's CNS lesions could not be sampled. Negative random skin biopsies coupled with biopsy-proven DLBCL and fluctuating vascular changes on MRA and cerebral angiogram make intravascular lymphoma less likely, though are not sufficient to rule out CNS vasculature involvement. In all 3 cases where lymphoma is diagnosed concurrently with HLH, treatment of HLH should precede lymphoma-directed therapy. Treatment for HLH with neurologic manifestations should include treatment of the underlying trigger and chemotherapy with CNS penetration.

The patient received high-dose dexamethasone followed by rituximab, cyclophosphamide, doxorubicin, vincristine, and high-dose intravenous methotrexate to treat DLBCL and associated HLH,[3] resulting in improved mental status and cognitive function. Repeat PET scan after 6 cycles showed a complete response. MRI Brain demonstrated decrease in T2 white matter abnormalities and her pancytopenia resolved. After finishing treatment, the patient was able to cook, clean, and garden. Twelve months after completing therapy, MRI brain shows persistent T2 hyperintensities, and she remains on multiple AEDs. Her post-treatment surveillance PET-CT scans continue to show no evidence of disease.

Commentary

We present a case of HLH due to DLBCL that presented with neurologic symptoms, pancytopenia, and migratory, steroid-responsive T2/FLAIR hyperintensities. Although the lack of brain tissue leaves open the possibility of secondary CNS lymphoma or secondary intracerebral, intravascular lymphoma underlying the patient's neurologic symptoms and neuro-imaging findings, this case highlights that the combination of neuro-inflammatory changes and systemic symptoms should prompt consideration of CNS-HLH. A multidisciplinary approach with hematology is essential for identifying a trigger and initiating effective treatment.

HLH is a rare, life-threatening condition characterized by dysregulated lymphocyte and macrophage activity leading to an excessive immune response. HLH is diagnosed either by proven genetic mutations in HLH-associated genes or by meeting 5 of 8 clinical criteria (Table 2). The majority of adult-onset HLH presents in response to infection, autoimmune disease, or malignancy. Ascertaining and treating the underlying trigger is both challenging and of utmost importance.[4-6] Malignancy-associated HLH accounted for 27-62% of adult HLH cases, the most common malignancy being NHL, and is associated with unfavorable overall survival compared to non-malignancy-associated cases.[7,8] Consensus guidelines suggest a thorough malignancy evaluation, including PET/CT and biopsy of suspicious lesions or repetitive tissue sampling.[6] One case series highlighted the challenges of identifying lymphoid malignancies in HLH hidden in unusual sites.[9] Pursuing additional or even repeat diagnostic testing in the face of negative or non-diagnostic results is important, particularly with new or progressive symptoms.

CNS-HLH is defined as patients meeting HLH diagnostic criteria and who have abnormal CSF profile and/or neuroimaging findings with or without neurological symptoms.[10] While 30-70% of pediatric patients with HLH had neurologic findings either at diagnosis or arising during their disease course,[10-12] the prevalence in adult-onset cases is less clear, ranging between 10-80% in retrospective analyses.[13-16] The neurologic symptoms of HLH are heterogenous, including altered mentation, seizures, cranial nerve palsies, headaches, meningismus, ataxia, and coma. Neuroimaging abnormalities are similarly heterogeneous, including multifocal white matter demyelination-like changes, large ill-defined confluent lesions, CNS hemorrhage, and leptomeningeal enhancement.[14-17] Elevated CSF protein

and CSF pleocytosis have been described.[13-15] While most patients with CNS-HLH exhibit systemic signs and symptoms, published reports describe patients who presented with isolated neurologic symptoms.[17-20]

Both HLH and its CNS manifestations are challenging diagnostic entities. HLH symptoms can be non-specific and patients may not exhibit all features on initial presentation.[4,5] In this case, the overlap of 2 differential diagnoses, 1) cerebral microhemorrhages and multifocal T2/FLAIR hyperintensities and 2) constitutional symptoms with cytopenia, and their steroid-responsiveness, were important clues. The differential diagnosis for cerebral microhemorrhages is broad, including ischemic cerebrovascular disease, cerebral amyloid angiopathy, hemorrhagic metastases, cerebral vasculitis, RLPS, thrombotic microangiopathies, intravascular lymphoma, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADSIL).[21,22] Superimposing cytopenias and constitutional symptoms, the patient's presentation is best unified by a systemic illness with neurologic manifestations. A subsequent broad serologic and radiologic evaluation led us to identify extra-neural sites for biopsy for accurate diagnosis of the HLH trigger. Because our patient's CNS lesions were inaccessible for biopsy, CNS involvement of DLBCL was never definitively excluded. The waxing and waning nature of our patient's symptoms temporally correlated with repeated steroids, which could have temporarily dampened immune activity associated with HLH or partially treated her underlying lymphoma. With the available data, her neurologic symptoms and neuro-imaging findings could be from CNS-HLH or secondary lymphoma with CNS or intravascular, intracerebral involvement.

The treatment of secondary CNS-HLH involves dampening the overactive systemic immune response and disease-targeted treatments. Treatment of the systemic immune response in adults is often based upon the HLH-94 protocol, which was adapted from a large prospective study of pediatric patients and involves use of dexamethasone, as in this patient, and the chemotherapy agent etoposide.[23] Concurrent malignancy-directed therapy should be initiated, and some experts recommend high-dose or intrathecal chemotherapy with CNS penetration in cases with neurologic involvement.[5] A similar strategy is used in cases lymphoma with secondary CNS involvement and concurrent HLH, including cancer-directed treatments, chemotherapy with CNS penetration, and quieting the immune system.

Overall, our case highlights the diverse spectrum of systemic and neurologic findings that can present in adult-onset HLH. Given the non-specific presentation, a high index of suspicion for HLH is needed in patients with unexplained neuro-inflammatory symptoms, particularly when systemic findings are associated. Identification of both the inflammatory syndrome and its underlying trigger are essential for accurate treatment in this fatal disease.

Authors' Note

This patient has provided written, informed consent for her medical history, treatment history, objective laboratory data, and images to be published in your journal and/or website. Importantly, the patient is aware that her medical information will be published without her name attached and understands that complete anonymity cannot be guaranteed. She also is aware that her right to revoke consent can occur at any time prior to publication, but once it has been committed to publication, it will not be possible to revoke consent. A copy of the signed consent form is available on request.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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