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Focal Neurological Involvement in Adult-Onset Still Disease-Associated Haemophagocytic Lymphohistiocytosis: A Diagnostic Challenge

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Abstract

A woman in her late 40s with adult-onset Still's disease (AOSD), previously independent in mobility, personal care, and cognition, presented with fever, sore throat, and a diffuse erythematous eruption involving the palms, soles, and lower limbs. Her medical history was also significant for established hepatitis B infection, for which she had been receiving long-term entecavir therapy. Her regular immunomodulatory medications included anakinra 100 mg subcutaneously once daily and methotrexate 20 mg subcutaneously weekly, alongside folic acid; prednisolone had recently been discontinued. Anakinra and methotrexate were temporarily withheld for one week on rheumatology advice due to concerns regarding COVID-19 infection. Investigations revealed marked hyperferritinemia, with ferritin peaking at 23,321 µg/L, hypertriglyceridaemia, hypofibrinogenaemia, liver dysfunction and a peak HScore of 214, a diagnostic scoring system for reactive haemophagocytic syndrome supporting a diagnosis of haemophagocytic lymphohistiocytosis (HLH), also termed macrophage activation syndrome (MAS) in the context of rheumatological disease. A SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) was positive; severe COVID-19 pneumonitis was considered a potential infectious trigger. The patient subsequently developed type 1 respiratory failure requiring admission to the intensive care unit (ICU). Despite treatment with corticosteroids and escalation of anakinra, her clinical course was complicated by profound encephalopathy, aphasia and focal neurological deficits. Magnetic resonance imaging (MRI) demonstrated left temporoparietal restricted diffusion and superficial pial enhancement, while ophthalmological assessment identified a right homonymous hemianopia. Electroencephalography (EEG) demonstrated persistent left hemispheric dysfunction. Despite extensive infectious investigations identifying potential contributing pathogens, no single definitive trigger for HLH/MAS could be established. National multidisciplinary review considered a broad differential diagnosis for the neurological abnormalities, including central nervous system involvement secondary to HLH, peri-ictal changes, cerebral ischaemia, viral infection and occult intravascular lymphoma. This case highlights the diagnostic complexity of HLH/MAS, in which multiple potential triggers and overlapping neurological manifestations may prevent identification of a single underlying aetiology despite extensive investigation. New-onset encephalopathy, aphasia, seizures or focal neurological deficits in patients with HLH/MAS should prompt early neurological assessment, appropriate MRI, EEG and cerebrospinal fluid investigations, and multidisciplinary specialist input. Neuroimaging findings should be interpreted alongside clinical, laboratory and other investigative findings, maintaining a broad differential diagnosis rather than prematurely attributing abnormalities to a single cause.

Categories: Neurology, Rheumatology, Infectious Disease
Keywords: adult-onset still disease, encephalopathy, focal motor seizures, haemophagocytic lymphohistiocytosis, hscore, macrophage activation syndrome

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome characterised by uncontrolled immune activation involving cytotoxic lymphocytes, macrophages and excessive pro-inflammatory cytokine release. In adults, HLH is commonly associated with infections, malignancies and immune-mediated disorders. When occurring in the context of rheumatological or autoinflammatory disease, HLH is frequently referred to as macrophage activation syndrome (MAS). Adult-onset Still's disease (AOSD) is a well-recognised condition associated with MAS/HLH [1-3].

Diagnosing HLH in adults remains challenging due to its overlapping clinical and laboratory features with sepsis, hepatic dysfunction and malignancy. Diagnostic frameworks, including the HLH-2004 criteria and the HScore developed by Fardet et al., are therefore interpreted alongside clinical judgement rather than relying on a single diagnostic test [1-4]. Although HLH is predominantly recognised as a systemic inflammatory disorder, neurological involvement may occur, presenting with altered consciousness, cognitive impairment,

aphasia, seizures, focal neurological deficits, and visual disturbances. Cerebrospinal fluid (CSF) and neuroimaging findings are variable, and normal CSF findings do not necessarily exclude central nervous system (CNS) involvement [5-7].

Restricted cortical diffusion and contrast enhancement on magnetic resonance imaging (MRI) are non-specific findings that may be associated with seizures, cerebral ischaemia, infection, vasculopathy, or malignancy [7,8]. Distinguishing between these potential aetiologies can be particularly challenging in critically ill, immunosuppressed patients, where multiple pathological processes may coexist. We present a case of AOSD-associated HLH/MAS complicated by encephalopathy, aphasia, focal motor seizures, weakness and homonymous hemianopia, alongside unilateral cortical and leptomeningeal MRI abnormalities. Despite extensive investigations and multidisciplinary specialist review, the relative contributions of inflammatory, infectious and vascular processes remained uncertain. This case highlights the importance of maintaining a broad differential diagnosis, undertaking targeted investigations and integrating multidisciplinary expertise when evaluating neurological deterioration in patients with HLH/MAS, while recognising that a definitive aetiology may remain elusive.

Case Presentation

Initial presentation and diagnosis of HLH/MAS

A woman in her late 40s with AOSD, previously independent in mobility, personal care and cognition, presented with fever, sore throat and a diffuse erythematous eruption involving the palms, soles and lower limbs (Figure *1*).



FIGURE 1: Diffuse erythematous cutaneous eruption during the hyperinflammatory episode, involving the left sole

Her regular medications included anakinra 100 mg subcutaneously once daily, methotrexate 20 mg subcutaneously weekly and folic acid; prednisolone had recently been discontinued. Anakinra and methotrexate were temporarily withheld for one week on rheumatology advice while infection was investigated. During admission, she developed supraventricular tachycardia at approximately 180 beats/minute, requiring adenosine and intravenous metoprolol.

Initial investigations demonstrated leukocytosis (18.6 × 10^9/L), rising C-reactive protein (CRP) (93-227 mg/L) and marked hyperferritinaemia, with ferritin peaking at 23,321 µg/L. Hypertriglyceridaemia, hypofibrinogenaemia, and elevated aminotransferases accompanied an increase in HScore from 132 to 214, supporting a diagnosis of HLH/MAS. Rheumatology restarted anakinra and administered intravenous methylprednisolone, with serial monitoring of inflammatory markers, liver function and coagulation parameters.

Respiratory and neurological deterioration

The patient subsequently developed worsening hypoxaemic respiratory failure with bilateral pulmonary opacities and pleural effusions. A SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) performed on hospital day 12 was positive, and severe COVID-19 pneumonitis was considered a potential infectious trigger for HLH/MAS. On approximately hospital day 20, she required intensive care admission and high-flow nasal oxygen.

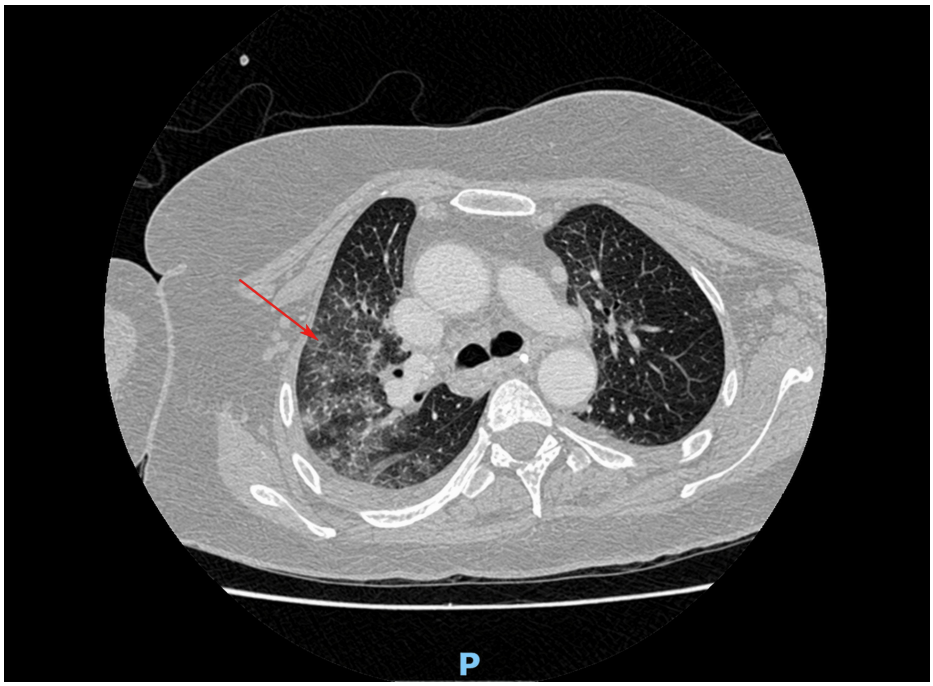


FIGURE 2: Contrast-enhanced CT of the thorax demonstrating extensive right-sided pulmonary consolidation with associated ground-glass opacities

Management involved local rheumatology, haematology, neurology, infection and critical care teams alongside a national HLH multidisciplinary team (MDT). Immunomodulatory treatment was intensified with high-dose dexamethasone and increased anakinra dosing. Cryoprecipitate was administered for hypofibrinogenaemia, with replacement thresholds subsequently adjusted following specialist advice. Co-trimoxazole and posaconazole were prescribed for opportunistic infection prophylaxis.

During respiratory deterioration, the patient developed profound encephalopathy, becoming minimally communicative, disorientated and unable to consistently follow commands. Aphasia and focal weakness subsequently became apparent. Serum ammonia was normal, and CT of the head demonstrated no acute intracranial abnormality. Although critical illness, delirium and medication effects were considered, these did not adequately explain the focal neurological findings.

Initial MRI demonstrated left occipitoparietal fluid-attenuated inversion recovery (FLAIR) hyperintensity, restricted diffusion and gyral enhancement, with subtler abnormalities involving the left middle frontal gyrus. Magnetic resonance angiography raised the possibility of an underlying vasculopathy (Figures *3*, *4*). Local neuroradiology review considered evolving cortical injury, potentially ischaemic, with appearances considered atypical for both vasculitis and neurological HLH.

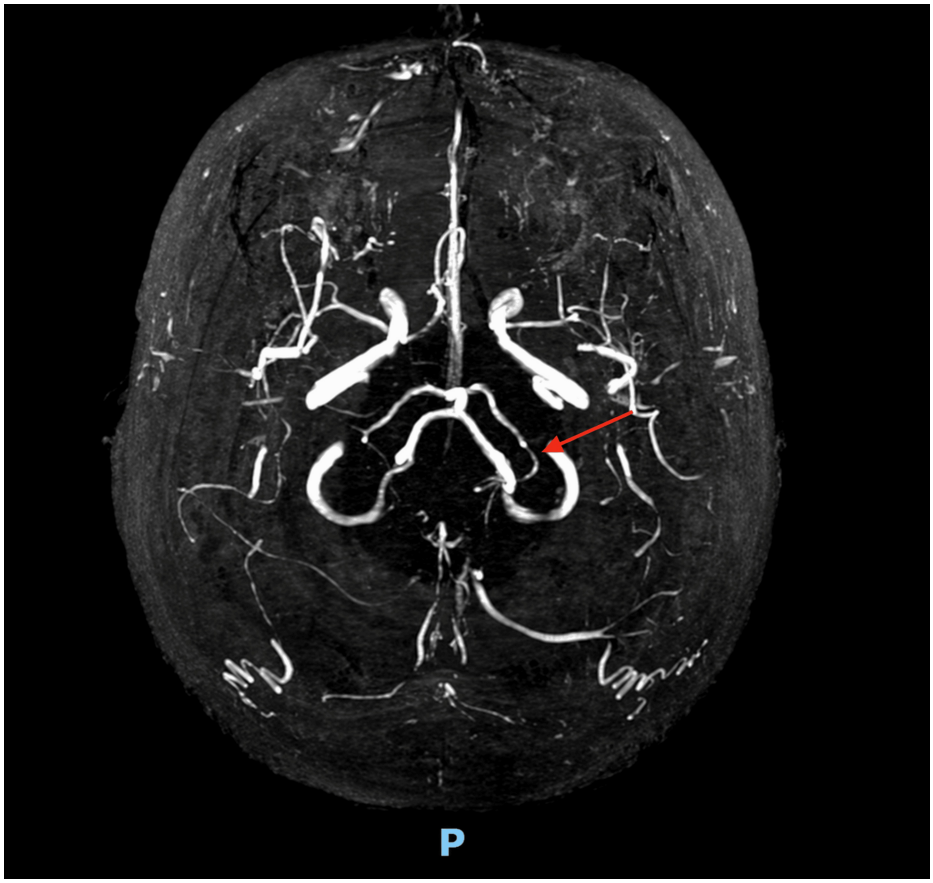


FIGURE 3: Axial time-of-flight magnetic resonance angiography of the intracranial circulation

Beading was observed within the left proximal posterior cerebral artery, with mild irregularity of the left internal carotid artery terminus and middle cerebral artery, raising suspicion of an underlying CNS vasculopathy

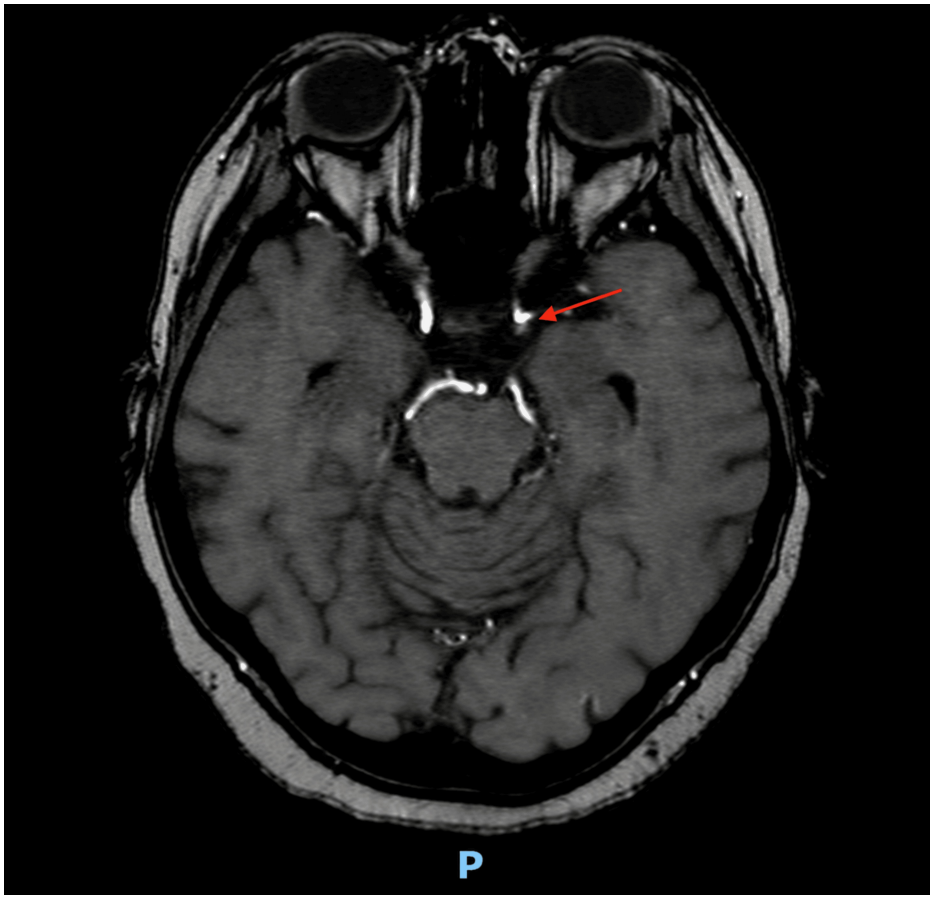


FIGURE 4: Axial time-of-flight MRI demonstrating suspected left-sided intracranial arterial irregularity

Mild irregularity of the left distal internal carotid artery and left proximal middle cerebral artery was observed, raising suspicion of an underlying CNS vasculopathy. The red arrow indicates the region of the reported vascular abnormality.

Subsequent national neuroradiology review characterised the dominant abnormality as a focal left temporoparietal superficial pial or leptomeningeal process, with enhancement predominantly involving surface structures (Figure *5*). Apparent interval progression was considered partly attributable to differences in contrast administration rather than definite radiological deterioration. The differential diagnosis included AOSD-associated inflammatory leptomeningitis, CNS involvement secondary to HLH/MAS, peri-ictal changes, ischaemic injury and an underlying lymphomatous process.

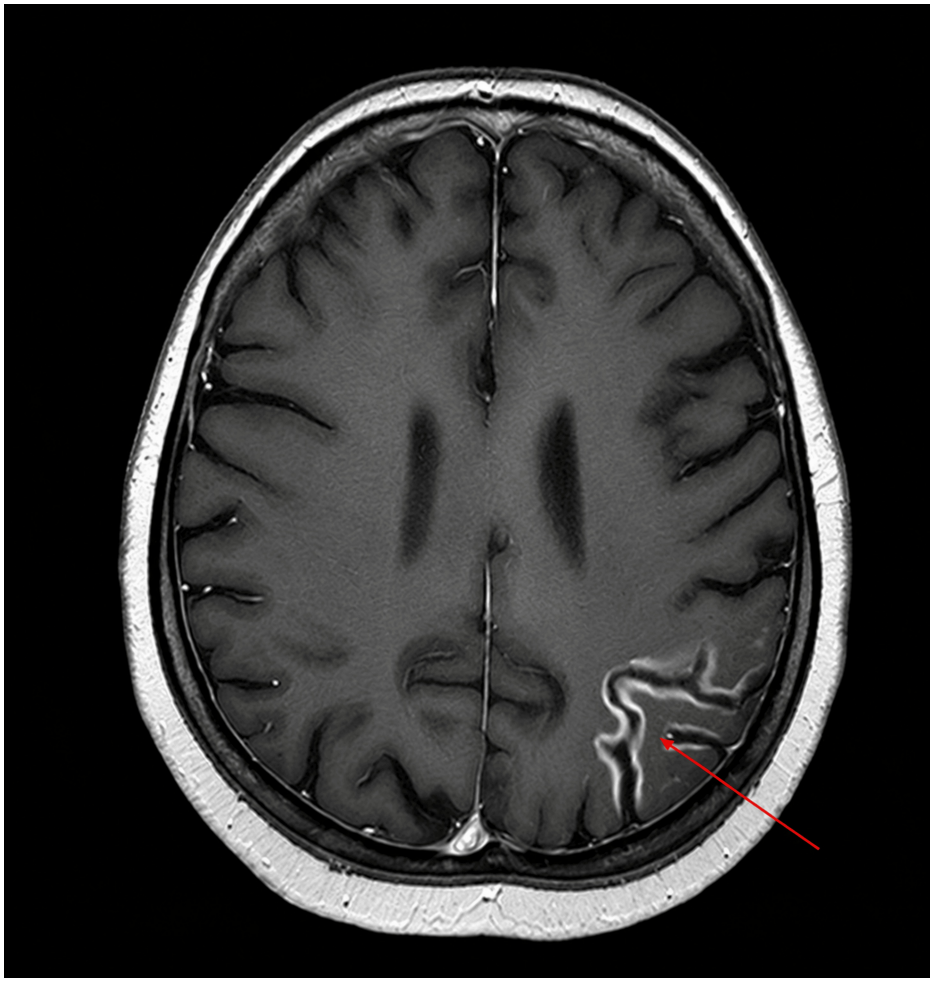


FIGURE 5: Axial T1-weighted post-contrast-enhanced brain MRI demonstrating left temporoparietal gyral and leptomeningeal enhancement

Abnormal gyral and superficial leptomeningeal enhancement in the left parieto-occipitotemporal region highlighted by the red arrow.

Serial electroencephalograms (EEGs) demonstrated persistent left-hemispheric dysfunction without ongoing epileptiform activity. Subsequent collateral history from the husband identified recurrent, stereotyped episodes of right-sided tonic and jerking movements involving the upper and lower limbs, lasting approximately 5-10 seconds. These episodes occurred intermittently over 7-10 days before resolving.

The concordance between the right-sided motor events, left-hemispheric EEG abnormalities, and left-sided MRI findings supported a clinical diagnosis of focal motor seizures. Peri-ictal changes were therefore considered a possible contributor to the MRI abnormalities, although they did not fully explain the superficial leptomeningeal enhancement. Levetiracetam was prescribed, but the patient and family subsequently declined continued treatment following resolution of the episodes. At the time of writing, on hospital day 70, genetic testing remained pending, and no further motor events were observed.

CSF and infectious investigations

Two lumbar punctures were performed, and extensive bacterial, viral, fungal, mycobacterial, autoimmune, and malignant investigations were undertaken. Epstein-Barr virus (EBV) was positive on PCR; however, infection specialists considered this insufficient to establish EBV encephalitis in the absence of corroborating CSF inflammation or systemic evidence. Both samples showed no pleocytosis, with negative herpes simplex virus (HSV) testing. Acyclovir was discontinued.

Blood and urine cultures were negative. Cytomegalovirus (CMV) serology was positive, and peripheral blood CMV PCR from day 56 demonstrated a viral load of 1,049 IU/mL. Specialist virology review considered this degree of CMV DNAemia unlikely to explain the marked liver dysfunction and recommended continued

monitoring without CMV-directed antiviral treatment at that stage.

The patient had established hepatitis B infection and had been receiving long-term entecavir therapy prior to admission, which was continued throughout hospitalisation. Hepatitis B serology on day 6 demonstrated confirmed hepatitis B surface antigen (HBsAg) positivity, hepatitis B core antibody (anti-HBc) positivity, negative anti-HBc IgM, negative hepatitis B e antigen (HBeAg), and positive anti-HBe, consistent with HBeAg-negative chronic HBV infection. HBV DNA remained detectable at 538 IU/mL on day 45. Specialist virology review recommended continuation of entecavir and consideration of discussion at the Viral Hepatitis MDT. There was insufficient evidence to establish HBV reactivation as the cause of the patient's clinical deterioration.

Biological and neurological course

Neurological recovery was gradual. The patient progressed from minimal communication and inability to follow simple instructions to producing meaningful short phrases in her first language. Speech and language assessment identified persistent expressive and receptive aphasia, with impaired comprehension, naming, repetition and writing. She required supported communication strategies and ongoing multidisciplinary rehabilitation.

Focal neurological examination remained limited by aphasia and variable engagement, with mild residual distal limb weakness. Subsequent ophthalmological assessment identified a right homonymous hemianopia, anatomically consistent with the left hemispheric abnormalities. Optical coherence tomography of the optic discs and maculae was unremarkable, and further ophthalmological assessment was arranged.

Following improvement in respiratory and neurological function, dexamethasone was reduced from 14 mg to 12 mg daily and anakinra from 200 mg three times daily to twice daily. This was followed by recurrent hypofibrinogenaemia, rising ferritin, and severe hypertriglyceridaemia. Fibrinogen fell to 0.87 g/L, and ferritin increased to 4,299 µg/L, prompting re-escalation of anakinra to 200 mg three times daily and administration of cryoprecipitate following specialist HLH multidisciplinary team recommendations in response to persistent hyperinflammatory activity.

The patient subsequently developed marked hepatocellular injury, with alanine aminotransferase (ALT) rising to 1,878 U/L and aspartate aminotransferase (AST) to 1023 U/L, despite a CRP of 2 mg/L on day 59 and ferritin of 2,330 µg/L measured on day 55. Triglycerides remained elevated at 7.4 mmol/L, with fibrinogen of 1.34 g/L (Table *1* and Figure *6*). Abdominal ultrasonography and liver MRI did not identify a structural explanation. Investigations considered hepatitis B reactivation, other viral infections, drug-induced liver injury, and recurrent HLH activity.

Hospital day	Ferritin (13–150 µg/L)	Triglycerides (<1.7 mmol/L)	Fibrinogen (1.5–4.0 g/L)	AST (0–35 U/L)	ALT (0–35 U/L)	CRP (0–5 mg/L)	Platelets (150–400 × 10^9/L)
0–2	23,321	4.4	1.99	58	–	93–227	–
20	–	9.2	1.52	138	35	61	124
26	–	10.9	1.78	183	33	23	171
32	3,454	14.9	1.52	–	–	–	292
33	–	20.4	1.61	–	–	–	322
40	–	13.1	1.23	176	170	<1	301
42	–	12.2	0.95	493	627	–	226
44	–	–	0.87	535	903	–	194
45	4,299	16.7	1.56*	–	724	<1	196
46	3,459	15.3	1.34	–	610	–	195
53	–	11.5	–	–	470	–	–
55	2,330	7.4	1.34	605	1,226	2	285
56	–	–	–	297	963	–	247
57	–	–	–	462	1,195	1	241
58	–	–	–	306	923	–	262
59	–	–	–	1,023	1,878	2	220
60	–	–	–	–	1,260	–	271
62	–	–	–	728	1,468	2	269
63	–	–	–	372	1,044	–	303
64	–	–	–	312	976	2	339
65	–	–	–	187	721	–	345
66	–	–	–	146	626	3	419
67	–	–	–	100	424	–	432
68	–	–	–	83	353	–	479
69	–	–	–	73	295	<1	525
70	–	–	–	–	230	–	–

TABLE 1: Chronological laboratory trends for selected biomarkers

Serial laboratory findings demonstrating marked hyperferritinaemia, progressive hypertriglyceridaemia, recurrent hypofibrinogenaemia, and subsequent hepatocellular injury. A dash indicates that no verified result was available. *Fibrinogen measured after cryoprecipitate.

ALT: alanine aminotransferase; ALP: aspartate aminotransferase; CRP: C-reactive protein

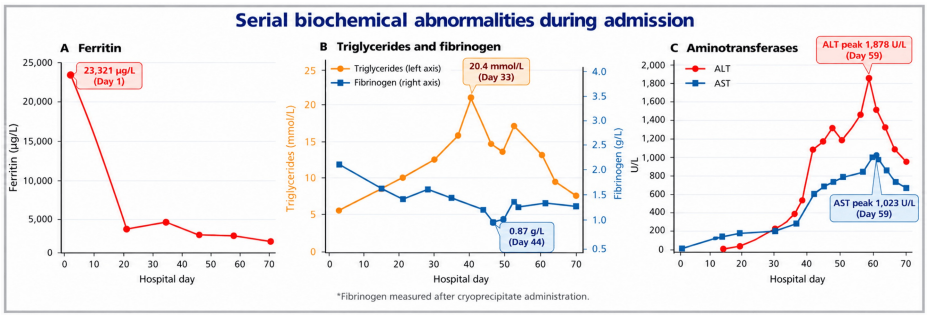


FIGURE 6: Biomarker trends throughout admission

Serial biomarkers demonstrating marked hyperferritinaemia, persistent hypertriglyceridaemia, recurrent hypofibrinogenaemia and later severe hepatocellular injury.

The HScore remained elevated at 207, although interpretation was complicated by ongoing treatment and evolving organ dysfunction. Despite biochemical deterioration, the patient remained afebrile and physiologically stable, with continued gradual neurological improvement.

Subsequent immunomodulatory management included baricitinib alongside dexamethasone and anakinra. By day 65, rheumatology documented overall clinical and biochemical improvement, including reductions in ferritin and liver enzymes. In view of this improvement, further adjustment of immunosuppression was planned, including gradual dexamethasone reduction, reduction of intravenous anakinra dosing and escalation of baricitinib to 4 mg daily, conditional on continued clinical stability.

Investigation for an occult inflammatory or malignant process

National HLH and neurology MDT discussions considered intravascular lymphoma as a potential underlying pathology given the recurrent hyperinflammatory syndrome and atypical neurological imaging findings. A deep skin biopsy was therefore performed to investigate this possibility. Histopathological results demonstrated no evidence of intravascular lymphoma. Although this finding reduced suspicion for an underlying intravascular lymphomatous process, it did not definitively exclude the diagnosis.

A bone marrow aspirate and trephine biopsy were performed on day 21 of admission. Flow cytometry showed no convincing evidence of clonal lymphoid or myeloid populations, while trephine morphology demonstrated non-specific reactive changes without evidence of neoplasia. Supplementary immunohistochemistry identified very rare CD163-positive histiocytes exhibiting haemophagocytosis. These findings provided additional support for HLH/MAS in the appropriate clinical context, without identifying an underlying haematological malignancy.

An AOSD-associated inflammatory leptomeningeal process remained an alternative explanation for the imaging abnormalities. Genetic testing for an underlying HLH predisposition was also initiated. Despite extensive investigations and specialist multidisciplinary input, the precise aetiology of the neurological syndrome remained unresolved.

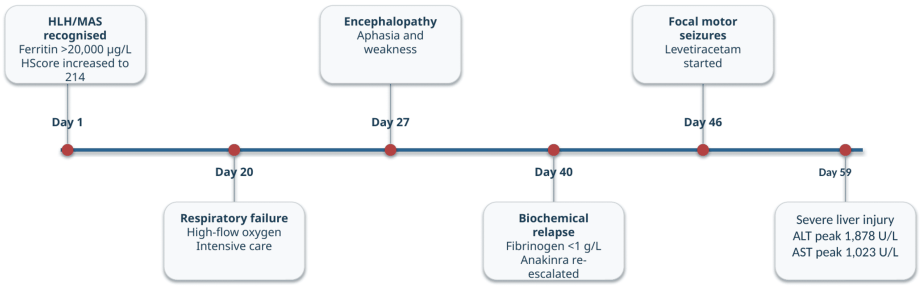


FIGURE 7: Clinical timeline of the admission, showing immunomodulatory treatment, respiratory course, neurological events, and key investigations by hospital day

HLH: haemophagocytic lymphohistiocytosis; MAS: macrophage activation syndrome; ALT: alanine aminotransferase; AST: aspartate aminotransferase

Discussion

This case illustrates two related but distinct diagnostic challenges: recognising HLH/MAS and identifying what triggered or sustained it. The systemic syndrome was supported by fever, marked hyperferritinaemia, hypertriglyceridaemia, hypofibrinogenaemia, liver dysfunction, bone marrow haemophagocytosis and a peak HScore of 214 [1-3]. AOSD provided a recognised autoinflammatory setting for MAS, but the presence of an underlying inflammatory disease did not remove the need to investigate infection, malignancy and genetic susceptibility [3-5,8].

Several potential contributors were present. Immunomodulatory treatment had recently been interrupted, prednisolone had been discontinued, and concurrent COVID-19 infection was identified. Each could plausibly have contributed to loss of inflammatory control, although their temporal relationships did not establish causation. Subsequent investigations introduced further uncertainty. EBV DNA was detected in CSF without pleocytosis or other convincing evidence of EBV encephalitis. CMV serology was positive, and peripheral blood CMV PCR demonstrated a viral load of 1,049 IU/mL. Specialist virology review considered this degree of CMV DNAemia unlikely to explain the marked hepatocellular injury and recommended continued monitoring without CMV-directed antiviral treatment at that stage. The patient also had established chronic HBV infection and had been receiving long-term entecavir therapy before admission. HBV DNA remained detectable at a low level during hospitalisation, with a viral load of 538 IU/mL on day 45. Although viral reactivation was considered in the context of substantial immunosuppression, the available findings did not establish CMV or HBV as the cause of the hyperinflammatory syndrome or liver dysfunction.

Malignancy was considered an important alternative driver of the hyperinflammatory syndrome. Lymphoma is a well-recognised cause of secondary HLH in adults and may remain occult despite initial imaging and bone marrow assessment [3,4,7]. In this case, the absence of convincing pathological lymphadenopathy or evidence of malignant infiltration on the available investigations reduced suspicion for an underlying malignancy. Nevertheless, recurrent hyperinflammation and atypical leptomeningeal imaging prompted the national MDT to consider intravascular lymphoma as a differential diagnosis. A deep skin biopsy was subsequently performed and demonstrated no histopathological evidence of intravascular lymphoma. Although this finding reduced suspicion for the diagnosis, a negative skin biopsy could not definitively exclude an underlying lymphomatous process.

The neurological syndrome added further complexity. In a single-centre study of 289 adults with HLH, CNS involvement was identified in 29 patients (10%); manifestations included altered consciousness, seizures, cranial neuropathies, memory disturbance, and limb weakness or paralysis [6]. Reported MRI abnormalities were heterogeneous and included cortical and subcortical lesions, white matter changes, and meningeal enhancement, while CSF findings were not uniformly abnormal [6]. The encephalopathy, aphasia, focal weakness, right homonymous hemianopia and suspected focal motor seizures in the present case were therefore compatible with neurological involvement in HLH/MAS, but were not specific for it.

Serial investigations narrowed the anatomical localisation without establishing the underlying mechanism. The right-sided motor episodes, persistent left-hemispheric EEG dysfunction, and left-sided cortical MRI abnormalities were concordant with a suspected left hemispheric seizure focus. Peri-ictal injury could account for some restricted diffusion and cortical signal change, but did not fully explain the superficial pial or leptomeningeal enhancement. Conversely, the imaging appearances were not considered typical of conventional vasculitis or a straightforward territorial infarction. National neuroradiology review initially

considered AOSD-associated inflammatory leptomeningitis, CNS involvement secondary to HLH/MAS, and lymphomatous infiltration within the differential diagnosis. Nevertheless, the precise mechanism underlying the neurological abnormalities remained unresolved, and CNS involvement secondary to HLH/MAS remained a possible explanation rather than a confirmed diagnosis.

The discordance between clinical and biochemical trajectories was also important. Neurological function and respiratory status improved while fibrinogen fell, ferritin and triglycerides increased, and severe hepatocellular injury developed. CRP was only 2 mg/L when ALT reached 1,878 U/L. A low CRP concentration and the absence of fever during corticosteroid and interleukin-1 blockade did not exclude ongoing hyperinflammatory activity. Serial assessment of ferritin, triglycerides, fibrinogen, blood counts, liver biochemistry, and organ function was therefore more informative than any single inflammatory marker [4,5,9]. The biochemical deterioration following reduction of dexamethasone and anakinra, and subsequent treatment re-escalation, further raised concern for ongoing immune activation, although treatment response alone could not establish its cause.

The principal lesson is not that every patient with AOSD-associated HLH/MAS requires every investigation performed in this case. Rather, investigation should remain broad, parallel, and responsive to the evolving phenotype. Adult recommendations emphasise simultaneous treatment of life-threatening hyperinflammation, systematic investigation of likely contributors and repeated reassessment with multidisciplinary input [3-5]. In this patient, rheumatology, haematology, infection, neurology, neuroradiology, gastroenterology and critical care teams successively refined the differential diagnosis, but did not identify a single unifying cause. The absence of a definitive trigger after extensive investigation does not necessarily represent diagnostic failure; it reflects the possibility that HLH/MAS may be multifactorial and that causal certainty may remain unattainable during the acute admission.

This report has several limitations. The suspected focal motor seizures were not captured electrographically, and no brain or meningeal tissue diagnosis was available. Although extensive investigations, including deep skin biopsy and virological testing, helped narrow the differential diagnosis, they did not establish the precise cause of the neurological abnormalities. Consequently, direct HLH/MAS involvement, AOSD-associated inflammation, peri-ictal injury and ischaemia remained possible explanations. Nevertheless, the longitudinal correlation of clinical findings, neuroimaging, EEG results and systemic biomarkers provides a detailed account of the diagnostic uncertainty encountered in adult HLH/MAS.

Conclusions

In AOSD-associated HLH/MAS, establishing the hyperinflammatory syndrome does not establish its trigger. Infectious, inflammatory, treatment-related, malignant and genetic contributors may coexist, and the first plausible abnormality should not end the diagnostic search. Positive viral tests require careful clinical interpretation, while negative investigations, including tissue biopsy, do not necessarily exclude occult malignancy.

Neurological deterioration in HLH/MAS may include encephalopathy, aphasia, focal weakness, seizures and visual-field loss, with heterogeneous and non-specific MRI, EEG and CSF findings. Treatment of life-threatening hyperinflammation should proceed alongside investigation of potential triggers, serial monitoring of HLH-related biomarkers and repeated multidisciplinary reassessment. Even after extensive investigation, a definitive trigger or unifying neurological diagnosis may remain unresolved; in this setting, diagnostic uncertainty should prompt structured follow-up rather than premature diagnostic closure.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Dimple Shamnani, Anisa Shakeel, Fatima Saad, Edmund Birkhamshaw

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Critical review of the manuscript for important intellectual content: Dimple Shamnani, Anisa Shakeel, Amaan Sajid, Fatima Saad, Edmund Birkhamshaw

Supervision: Edmund Birkhamshaw

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all

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Data are available on reasonable request. The data are stored as de-identified participant data which are available on request to dimpleshamnani.ds@gmail.com

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