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Case Report

Hemophagocytic lymphohistiocytosis secondary to diffuse large B-cell lymphoma presenting with recurrent multi-territory infarcts: A case report[☆]

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ABSTRACT

Lymphoma-associated hemophagocytic syndrome is a life-threatening disease with poor prognosis and may present as ischemic stroke. We report a case of a 56-year-old female with recurrent multi-territory infarcts caused by diffuse large B-cell lymphoma with secondary hemophagocytic lymphohistiocytosis. She had been diagnosed with ischemic stroke and hemophagocytic syndrome probably secondary to Epstein-Barr virus infection 3 months previously and treated with Dexamethasone and Aspirin. High resolution vessel wall magnetic resonance imaging showed vessel wall thickening at some intracranial vessels suggesting vasculitis. Abdominal computed tomography scan revealed splenomegaly, multiple bilateral small nodules of the lung, multiple liver lesions, multiple bilateral renal masses, gastric wall thickening and multiple nodules in the omentum. Cerebrospinal fluid cytology showed increased cerebrospinal-fluid protein level. Hemophagocytosis was showed on bone marrow aspirate cytology. Gastric tissue biopsy revealed large B cell lymphoma. Chemotherapy was not given because the patient had severe pneumonia and sepsis. The patient died 28 days after the definitive diagnosis was confirmed. Ischemic stroke in our patient with diffuse large B-cell lymphoma may be due to vasculitis or intravascular large B-cell lymphoma.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an infrequent but potentially life-threatening hyperinflammatory

syndrome, including impaired function of cytotoxic T lymphocytes and natural killer (NK) cells, as well as macrophages [1]. The secondary form of HLH is most often observed in adults and has a wide range of etiologies including all types of infections (i.e., viral, bacterial, parasitic, fungal, and mycobacterial), malignancies (eg, T-cell/natural killer cell lymphomas, Hodgkin lymphoma, multiple myeloma,..), and acquired immunodeficiency (eg, HIV/AIDS, transplantation, chemother-

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apy,..) [2]. HLH in the context of malignancy is considered as a big challenge to clinicians due to variable overlaps of symptoms with other types of HLH, sepsis and multiorgan failure, therefore resulting in higher incidence of misdiagnosis and mortality. However, few reports currently focus on the malignancy-associated HLH due to low incidence and insufficient knowledge. We report the case of a 56-year-old woman with HLH involving hematologic malignancies (diffuse large B-cell lymphoma) who presented with the clinical features of recurrent multi-territory infarcts.

Case report

A 56-year-old Vietnamese woman presented to Blood Transfusion Hematology Hospital in February 2019 because of prolonged fever and fatigue. Her initial complete blood count (CBC) on admission was notable for severe anemia: hemoglobin (Hb) 60 g/L (120–175 g/L), mean corpuscular volume 72.9 fL (78–100), white blood cell count 9.65 G/L (4–10 G/L), neutrophils 55% (45%–75%), lymphocytes 20 % (20%–35%), monocytes 20% (4%–10%), platelet count 193 G/L (150–450 G/L). Human immunodeficiency virus (HIV) antibody, antinuclear antibody (ANA), Anti-double stranded DNA antibody (Anti ds-DNA), rheumatoid factor (RF), Coombs tests were negative. Other laboratory test results showed hypertriglyceridemia (565.49 mg/dL) (40–166 mg/dL), hyperferritinemia (3153.84 ng/ml) (10–280 ng/ml), increased soluble CD25 levels (3316.936U/ml) (Normal < 511.364 U/ml) and elevated lactate dehydrogenase (LDH) (592.34 U/L) (Normal < 248 U/L). Epstein-Barr virus (EBV) Detection by PCR (Polymerase Chain Reaction) result was positive. A lumbar puncture was performed which showed 14 white blood cell; 6 red blood cells; protein of 32.6 mg/dl (Normal < 45 mg/dL); glucose of 3.58 mmol/L (2.2–3.9 mmol/L) (serum glucose of 5.3 mmol/L) and Mycobacterium tuberculosis detection by PCR result was negative. Bone marrow aspirate cytology revealed red blood cell and platelet phagocytosis. Abdominopelvic CT scan and brain MRI were obtained showing hepatomegaly, splenomegaly and subacute bilateral pontine infarction (Fig. 1). Gastrointestinal and colorectal endoscopy were performed with unremarkable results. The diagnosis was established with Hemophagocytic syndrome probably secondary to Epstein-Barr virus (EBV) infection - Pontine infarction. The patient was treated with Aspirin (81mg/day) and Dexamethasone (5 mg/day). The fever was controlled and anemia improved partially over the next several weeks. She was continuously treated with Aspirin (81 mg/day) and Dexamethasone (2 mg/day) after discharge from the hospital.

In May 2019, the patient was admitted to University Medical Center – Ho Chi Minh city due to acute weakness at the left side and slurred speech. She presented an expressive language impairment, short-term and long-term memory deficit, left central facial palsy and quadriparesis. CBC showed anemia, mild thrombocytopenia: WBC count 13.39 G/L (4–10 G/L), Hb 96 g/L (120–175 g/L), Platelets 142 G/L (150–450 G/L). Brain MRI showed multifocal cerebral infarcts located at left frontal lobe and bilateral corona radiata (Fig. 1). However, magnetic resonance angiography (MRA) of the brain

revealed normal intracranial vasculature. Holter monitor, echocardiography, carotid Doppler, lower extremity venous Doppler ultrasound results were unremarkable. Cerebrospinal fluid (CSF) examination showed 19 white blood cell; 2000 red blood cells; protein of 95.22 mg/dL (Normal < 45 mg/dL); glucose of 3.6 mmol/L (2.2–3.9 mmol/L) (serum glucose of 6 mmol/L (3.9–6.4 mmol/L)), Lactate 4.139 mmol/l (1.1–2.4 mmol/L). Other CSF studies including CFS culture looking for bacteria and fungi, Herpes Simplex virus (HSV) PCR test, GeneXpert for the detection of Mycobacterium tuberculosis were all negative. The patient was treated with Dexamethasone and Plavix (75 mg/day) and discharged 7 days after the admission.

Ten days after discharge, the patient was readmitted with deteriorated neurological condition as noted by developing quadriplegia and a worsening level of consciousness. On examination at the time of admission, she was agitated and had visual hallucinations. Concurrently, she had developed low-grade fever without an identifiable source of infection. Laboratory tests showed anemia, thrombocytopenia: WBC count 9.01 G/L (4–10 G/L), Hb 78 g/L (120–175 g/L), Platelets 122 G/L (150–450 G/L) and elevated LDH (300 U/L) (Normal < 248 U/L). Brain MRI showed some recent small subcortical infarcts located at left frontal lobe when comparing with the brain MRI 2 weeks earlier. Intracranial high resolution vessel wall magnetic resonance imaging (HR-vwMRI) post-contrast T1W showed vessel wall thickening with moderate enhancement at the left PCA and bilateral MCA segments relevant to the cerebral infarction suggesting vasculitis (Fig. 2). Lumbar puncture was performed again and CSF examination showed: 13 white blood cell, neutrophils 10%, lymphocytes 90 %, 0 red blood cells; protein of 111.08 mg/dL (Normal < 45 mg/dL); glucose of 5.2 mmol/L (2.2–3.9 mmol/L) (serum glucose of 8.9 mmol/L (3.9–6.4 mmol/L)); lactate 4.139 mmol/L (1.1–2.4 mmol/L). CSF culture looking for bacteria and fungi, GeneXpert for the detection of Mycobacterium tuberculosis were all negative. An abdominal, pelvic and thoracic CT-Scan revealed splenomegaly, multiple bilateral small nodules of the lung, multiple liver lesions, multiple bilateral renal masses, gastric wall thickening and multiple nodules in the omentum (Fig. 3). Red blood cell and platelet phagocytosis was showed on bone marrow aspirate cytology. Gastrointestinal endoscopy was performed again showing mild congestive gastritis and Kaposi's sarcoma was doubted. The pathological findings of gastric tissue biopsy revealed large B cell lymphoma (Fig. 4). The patient was planned to start on chemotherapy but she developed septic shock from severe pneumonia and died 28 days after the definitive diagnosis.

Discussion

HLH is diagnosed clinically by either 1) having a proven genetic mutation known to be associated with HLH or 2) fulfilling 5 out of 8 clinical criteria: (i) fever; (ii) splenomegaly; (iii) cytopenia involving at least 2 of the 3 lineages in the peripheral blood-hemoglobin <90 g/l, platelets <100 × 10⁹/l, neutrophils <1.0×10⁹/l; (iv) hypertriglyceridemia (≥3.0 mM) and/or hypofibrinogenemia (≤1.5 g/l); (v) hemophagocytosis in bone

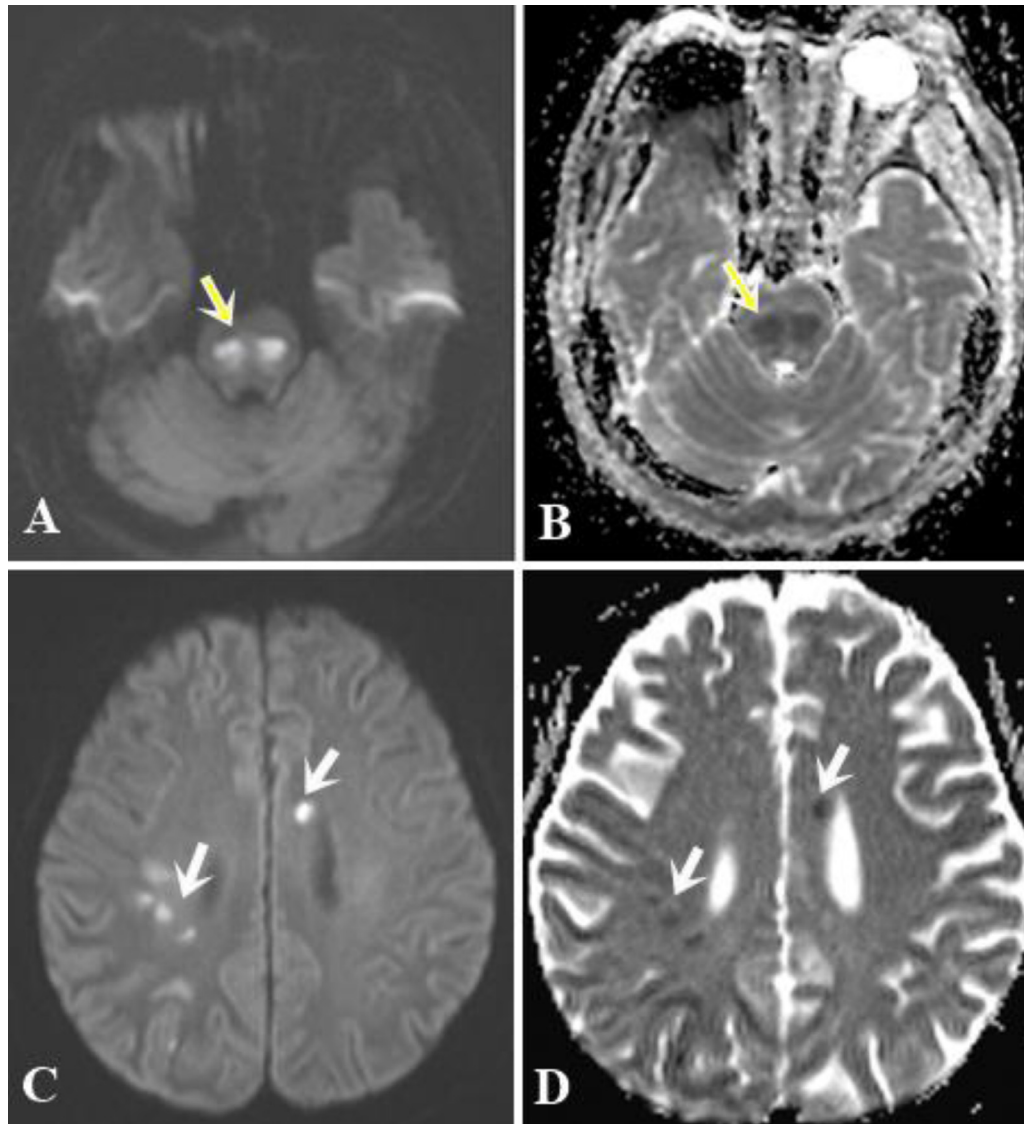


Fig. 1 – Brain MRI of the first admission revealed acute pontine infarction with high signal intensity on DWI (A) and hypointensity on apparent diffusion coefficient map (B) (yellow arrows); Repeat brain MRI of the second admission showed multifocal cerebral infarcts located at the left frontal lobe and bilateral corona radiata (C and D, white arrows).

marrow, spleen, or lymph nodes; (vi) low or absent natural killer (NK) cell activity; (vii) hyperferritinemia ($\geq 500 \mu\text{g/l}$); and (viii) increased soluble CD25 levels ($\geq 2400 \text{ U/ml}$) [1,3–5]. Our patient had 6 of the 8 clinical criteria: fever, splenomegaly, hypertriglyceridemia, hyperferritinemia, increased soluble CD25 levels, and hemophagocytosis in bone marrow. The most common causes of secondary HLH in adults are infections (49%), neoplasms (27%), rheumatoid arthritis (7%), and immunodeficiencies (6%) [6]. On the first admission to Blood Transfusion Hematology Hospital, with negative results on autoimmune screening tests, full body CT Scan and digestive system endoscopy, the patient was diagnosed with HLH probably secondary to Epstein-Barr virus (EBV) infection because of positive result on EBV detection by PCR. At this time, the patient recovered with high-dose steroid treatment. Pontine infarction was coincidentally found with the result of brain MRI and the

patient was treated with Aspirin for recurrent stroke prevention.

Three months later, despite continuous treatment with Dexamethasone and Aspirin, the patient had acute neurologic symptom due to ischemic stroke and readmitted to hospital. Complete evaluation for stroke risks including large-artery atherosclerosis, cardioembolism, hypercoagulable disorders, and cerebral vasculitis was performed but failed to determine the etiology of stroke. Aspirin was replaced by Clopidogrel taken along with Dexamethasone. 17 days after the admission, the patient's neurological condition deteriorated and accompanied with fever. Development of HLH is commonly associated with hematologic malignancies, often non-Hodgkin lymphoma [7]. The clinical suspicion regarding the etiology of recurrent stroke was vasculitis due to HLH secondary to lymphoma. After the result of gastric tissue biopsy along with the

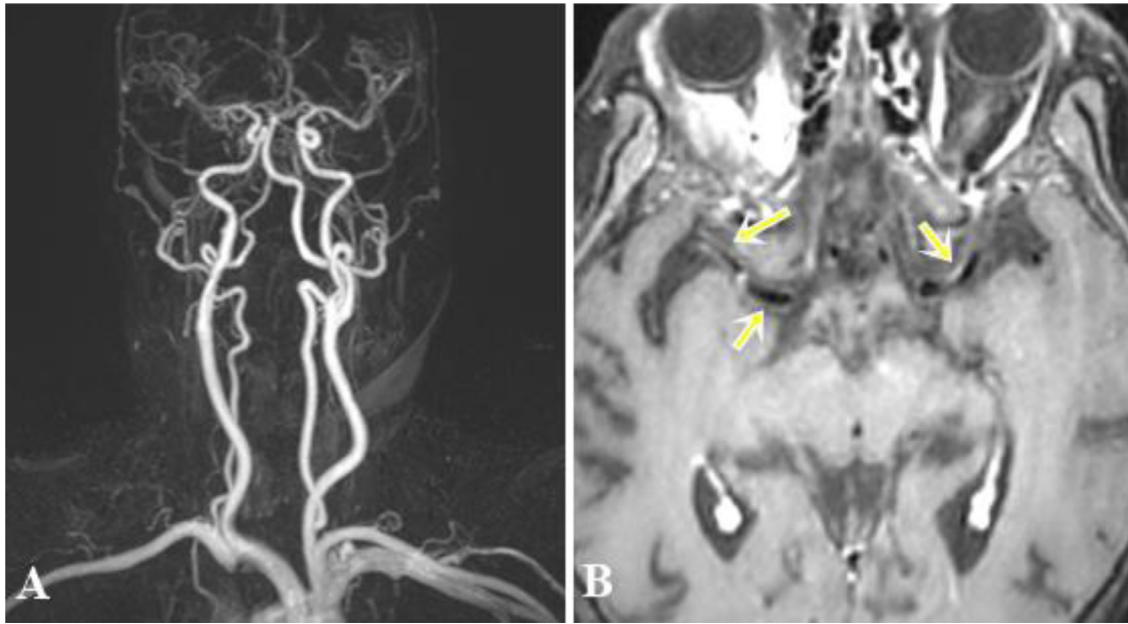


Fig. 2 – MRA of the brain revealed unremarkable intracranial vasculature (A); HR-vw MRI post-contrast T1W showed vessel wall thickening with moderate enhancement of bilateral MCA segments relevant to the cerebral infarction suggesting vasculitis (B) (yellow arrows).

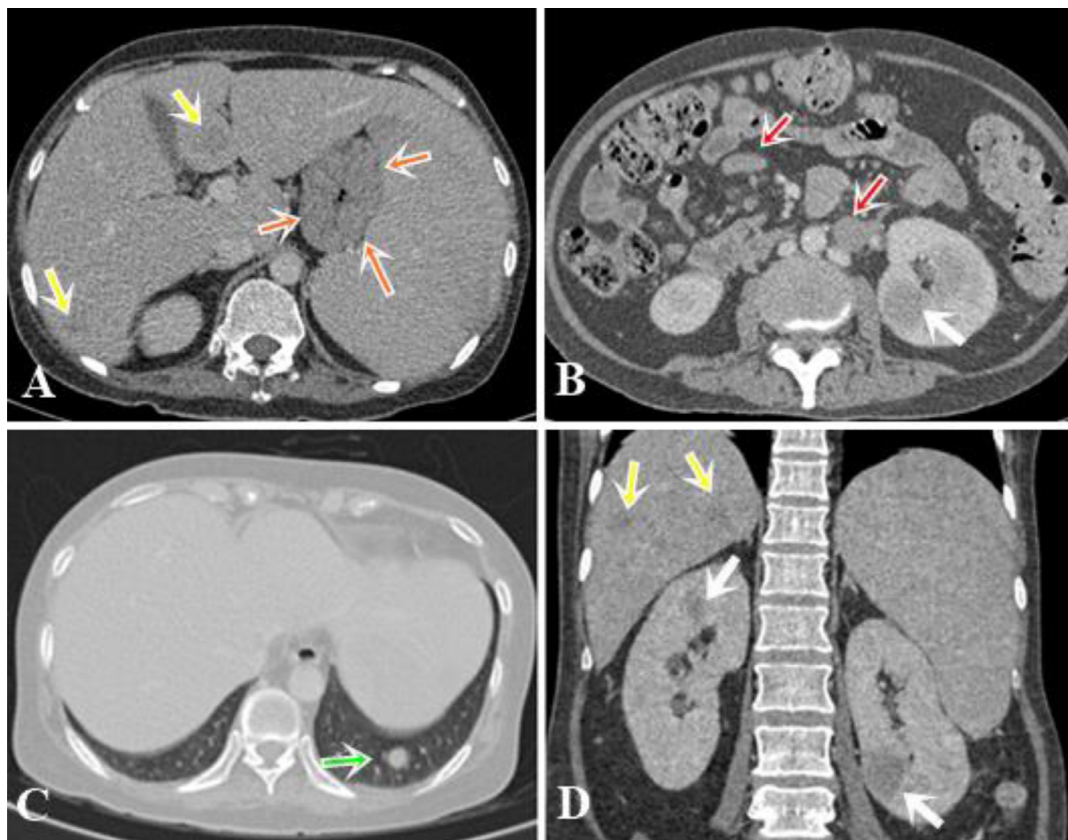


Fig. 3 – An abdominopelvic and thoracic CT scan revealed splenomegaly (A, red arrows); multiple liver lesions (B, yellow arrows); multiple bilateral small nodules of the lung (C, green arrows); multiple bilateral renal masses (D, white arrows).

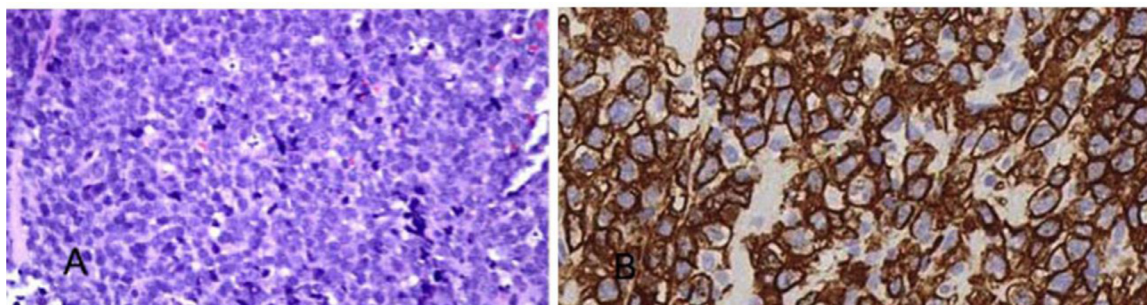


Fig. 4 – The pathological findings of gastric biopsy revealed large B cell lymphoma. Diffuse infiltration of large lymphoid cells with prominent nucleoli and brisk mitosis (A, H&E stain, magnification $\times 200$). The tumor cells showed strong expression of CD20 (B, immunohistochemical stain, magnification $\times 400$).

result of CT scan, definitive diagnosis was established with HLH secondary to diffuse large B-cell lymphoma. Our patient presented with multistage intraparenchymal infarcts indicating central nervous system (CNS) vasculitis supported by HR-vwMRI. Typical features for CNS vasculitis are inflammatory damage of vessel walls and vascular thrombosis. Progressive neurological deficits observed in CNS vasculitis are frequently associated with cerebral and spinal ischemic lesions on MRI and CT scans. According to Song et al., CNS vasculitis imaging findings may mimic intravascular large B-cell lymphoma IVBCL [8,9]. Increased serum lactate dehydrogenase (LDH) as seen in our patient is observed in over 80% of all cases with IVBCL [10,11]. Generally, both IVBCL and CNS vasculitis may respond to corticosteroid therapy, although the treatment effect is almost exclusively transient in IVBCL [12]. In our patient case, we planned for chemotherapy and brain biopsy. However both brain biopsy and chemotherapy were delayed because the patient got severe pneumonia and died for septic shock 28 days after the definitive diagnosis.

Conclusion

Recurrent ischemic stroke in our patient with diffuse large B-cell lymphoma may be due to vasculitis or IVBCL. Although being a rare disease, our case should raise the alertness for consideration of IVBCL as a differential diagnosis. When diagnosis of IVBCL is doubtful, we propose early brain biopsy or random skin biopsies, even without clinically apparent cutaneous involvement.

Patient consent

The protocol was reviewed and approved by the Human Research Ethics Committee of the University of Medicine and Pharmacy at Ho Chi Minh City. The study was performed in accordance with the Declaration of Helsinki. The patient wrote informed consent.

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