

Table 1. Investigations.

LAB PARAMETERS	REFERENCE RANGE	FIRST ADMISSION IN MAY 2022	READMISSION IN SEPTEMBER 2022
Blood investigations			
Haemoglobin	12-18g/dl	12	5.5
Platelets	150 × 10 ³ - 450 × 10 ³ /μl	200	70
White cell counts	4 × 10 ³ - 9 × 10 ³ /μl	10	8.4
Sodium	135-145 mmol/l	135	130
Potassium	3.5-5.1mmol/l	4	3.3
Urea	2.8-7.2 mmol/l	5	4.3
Creatinine	59-104 μmol/l	60	49
Corrected calcium	2.2-2.65 mmol/l	2.32	2.42
Total protein	66-83 g/l	70	71
Albumin	35-52 g/l	30	19
Globulin	28-36 g/l	40	57
Total bilirubin	5-21 μmol/l	15	16.6
Alanine transferase	0-50 U/l	20	18
Alkaline phosphatase	30-120 U/l	100	107
LDH	105-333 U/l	400	1,185
Magnesium	0.73-1.06 mmol/l	0.75	0.69
Inorganic phosphate	0.81-1.45 mmol/l	1	0.93
Erythrocyte sedimentation rate	0-20 mm/hour	60	78
C-reactive protein	<5mg/l	50	191
Blood culture	No growth	No growth	No growth
HIV/VDRL/hepatitis B/ hepatitis C	Non-reactive	Non-reactive	Non-reactive
ANA	Negative	Positive 1:320 (atypical speckled)	Negative
Complement 3	0.1-0.4g/l	0.248	
Complement 4	0.9-1.8g/l	1.191	
Extractable nuclear antibodies Anti-Ds DNA Anti- Jo 1 Anti-Scl 70 Anti-smith Anti-RNP Anti-Ro Anti-La	Negative	All negative	
P-ANCA C-ANCA	Negative	Both negative	
Paraneoplastic panel (anti-YO, anti-HU, anti-Ri, anti-Ma2, anti-Tr, anti-GAD)	Negative	All negative	
Coombs test	Negative		Negative
PBF		Normal	Bicytopenia. No blasts. Hypochromic microcytic anemia possible iron deficiency anemia.
B12	145-569 pmol/l	677	
Folate	10.4- 78.9 nmol.l	>42.9	
Thyroid function test TSH T4	0.35-4.94mIU/l 9.01-19.05pmol/l	2.03 13.02	
Iron study Ferritin Iron Total iron binding capacity (TIBC) Transferrin saturation	13-150 μmol/l 5.8-34.5 μmol/l 23-70 μmol/l 16%-45%		1,161 3.2 23 14

Continued

LAB PARAMETERS	REFERENCE RANGE	FIRST ADMISSION IN MAY 2022	READMISSION IN SEPTEMBER 2022
Bone Marrow Aspirations (BMA)			Marrow tissues with diffuse infiltration by abnormal lymphoid cells with only sinusoidal involvement of the interstitium and they are positive for CD79a, CD20, MUM-1, CD138, Bcl2, Bcl6, Ki67 > 90% and CD5 which are consistent with High Grade Mature B Cell Lymphoma GCB Type.
Cerebrospinal fluid			
Cell count	0	0	
Cryptococcal antigen	Negative	Negative	
Glucose	2.2-3.9mmol/l	3	
Protein	0.15-0.45g/l	0.64	
Globulin	Negative	Positive	
Appearance	Clear	Clear	
Acid fast bacilli (AFB)	No AFB	No AFB	
Mycobacterium culture	No growth	No growth	
Culture	No growth	No Growth	
Japanese encephalitis PCR	Not detected	Not detected	
Herpes simplex virus PCR	Not detected	Not detected	
varicellar zoster virus PCR	Not detected	Not detected	
Flavivirus PCR	Not detected	Not detected	
Cytology		Occasional lymphocytes seen, no malignant cells.	

vomiting. Her family members did not know of any history of focal neurological deficit, myoclonus, or prior comorbidity. She was restless and her Glasgow Coma Scale remained eye-opening at 4, verbal 2, and motor 5 postictally. General physical examination was unremarkable. A neurological examination revealed that she was confused and uncooperative for a higher mental function examination. Overall cranial nerves examination was normal. Power, tone, and deep tendon reflexes of upper and lower limbs were normal. Frontal release signs, including bilateral grasp and snout reflexes, were elicited. Extrapyramidal, cerebellar, and autonomic examinations were unable to be carried out without the patient’s cooperation. An urgent lumbar puncture was done to rule out meningoencephalitis after a normal computed tomography brain finding. Cerebrospinal fluid (CSF) opening pressure was 16 cmH₂O while her CSF analysis was aseptic with minimally raised protein level and normal glucose ratio (Table 1). CSF venereal disease research laboratory and viral studies were negative. Antinuclear antibody (ANA) was found to be positive 1:320 (atypical speckled pattern). However, she did not meet the criteria for systemic lupus erythematosus. The remaining autoimmune workup was negative, and she has no clinical signs of autoimmune diseases. Her hepatitis B, hepatitis C, HIV, and paraneoplastic screen were negative. She underwent an electroencephalogram (EEG) as her seizures remained poorly controlled. The EEG showed cortical dysfunction with occasional sharp waves at the right frontoparietal region. Magnetic resonance imaging (MRI) of the brain (Figure 1) revealed non-enhanced biparietal lobe hyperintensities and focal hyperintensities over the right corpus callosum and adjacent right frontal horns associated

with microhemorrhages which may suggest encephalitis or ischemia. She was unable to recognize her family members including her husband. She remained disorientated for a few weeks and subsequently slowly regained her alertness upon discharge. She was discharged with antiseizure medications (T. Levetiracetam 1.5 g BD, C. Phenytoin 300 mg ON, and T. Sodium Valproate 600 mg BD) after having completed treatment for presumed viral encephalitis.

A month later, she was readmitted to the intensive care unit for status epilepticus. Her altered sensorium recurred. We noticed that she had new onset of bicytopenia (hemoglobin 5.5g/dl, white cell counts $8.4 \times 10^3/\mu\text{l}$, platelets $70 \times 10^3/\mu\text{l}$) with lactate dehydrogenase (LDH) of 1185 IU/l. Physical examination did not reveal any palpable lymphadenopathy or hepatosplenomegaly. An urgent peripheral blood film (PBF) did not find any blasts. We then proceeded with bone marrow aspirations and trephine biopsy (Figure 2), and indeed it showed marrow tissues with diffuse infiltration by abnormal lymphoid cells with only sinusoidal involvement of the interstitium and they are positive for CD79a, CD20, MUM-1, CD138, Bcl2, Bcl6, Ki67 > 90%, and CD5 which are consistent with high-grade mature B cell lymphoma germinal center B-cell Type. In view of only sinusoidal involvement in the trephine biopsy, IVLBCL is highly suggested. Contrast-enhanced computed tomography Thorax, abdomen, and pelvis were arranged and were negative for distant metastasis or lymphadenopathy. She was then referred to the hematology team and started on Rituximab cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) therapy. Of late, her condition is stable without seizures, and her confusion is improving.

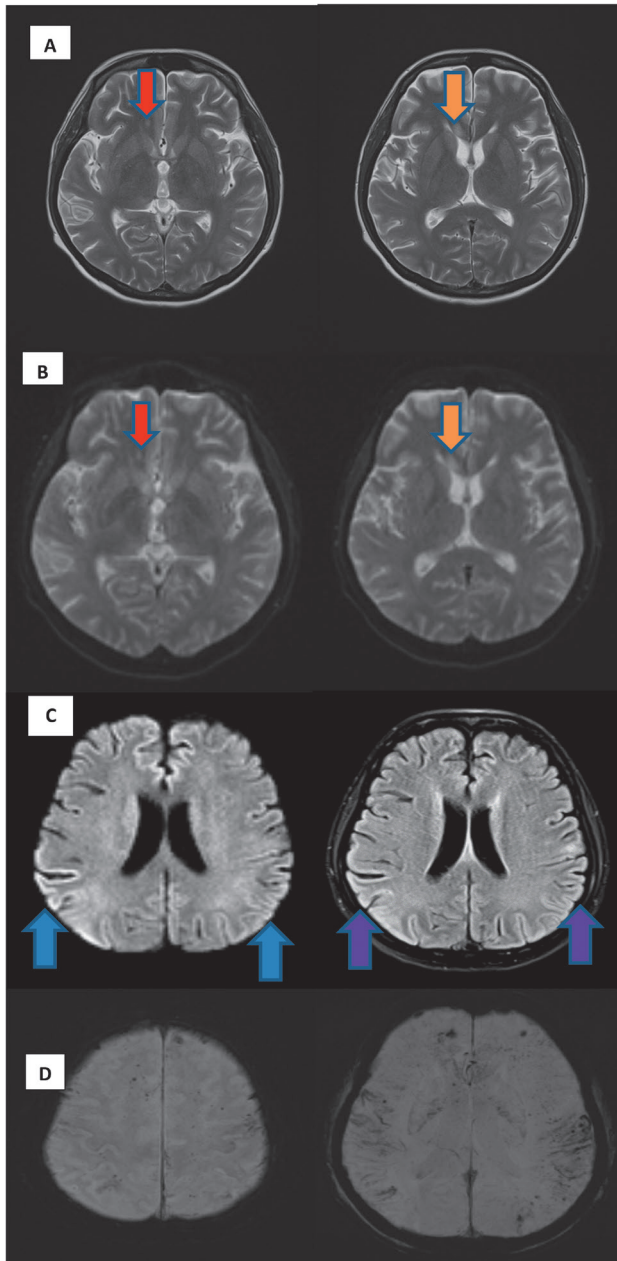


Figure 1. (A) MRI brain T2 weighted showed high signal in the right frontal white matter (red arrow) and right genu of corpus callosum (orange arrow). (B) These lesions at right frontal white matter (red arrow) and right genu of corpus callosum (orange arrow) also demonstrated high signal in DWI acquisitions. (C) MRI brain showed high signal in the gyri at bilateral parietal lobes (blue and purple arrows) in DWI (left) and FLAIR (right) acquisitions. (D) MRI brain susceptible weighted imaging acquisitions showed multiple blooming artifacts in keeping with microhemorrhages.

Discussion

IVLBCL is a rare clinical entity with heterogeneous clinical manifestations. There is selective growth of cancerous and atypical cells in the small and intermediate-sized vessels in various organs such as the CNS, lungs, skin, adrenal gland, liver, kidney, spleen, bone marrow, thyroid, pituitary, and gastrointestinal tract [4]. Diagnosis is made by organ biopsy and random skin biopsy from the uninvolved site in patients who presented with pyrexia of unknown origin [4]; 7 out of 32 patients with pyrexia of unknown origin

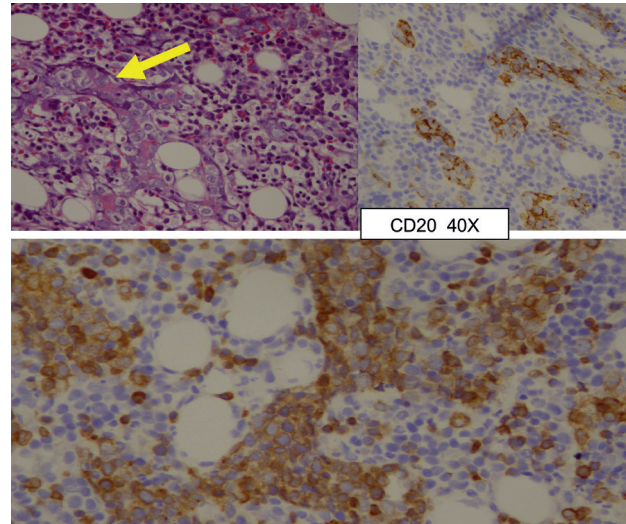


Figure 2. Marrow tissues show diffuse infiltrations by abnormal large lymphoid cells within sinusoid (yellow arrow) which are arranged in chords and aggregates, display moderate amount of cytoplasm, round nucleus, open chromatin pattern, and prominent nucleoli and they showed CD20 and CD79a positivity.

who had random skin biopsies from unaffected sites were diagnosed to have IVL, according to Sitthinamsuwan et al. [5]. One-quarter of patients experienced early neurological manifestation in the form of altered sensorium, focal neurological deficit, dementia, and seizure. Our patient here had an initial neurological presentation which has led us to the investigation of neurological diagnosis. However, progressive reduction in blood cell count and raised LDH level as seen in our case report are telltale signs of IVLBCL [4].

Current literature shows that IVLBCL tends to affect elderly patients aged 60-70 years old, with a male-to-female ratio of 1:2. It has been suggested that the incidence of IVLBCL is increased in Asian populations [6]. Our patient here is a middle-aged Thai lady who came in with seizures and altered sensorium. Initial diagnoses considered are usually stroke, encephalomyelitis, vasculitis, and multiple sclerosis. Therefore, many IVLBCLs are diagnosed at autopsy. MRI has been shown to be the best modality despite its low level of sensitivity and specificity. Hyperintense cortical or subcortical lesions on T2-weighted and fluid-attenuated inversion recovery imaging suggest small vessel ischemia, demyelination, or vasculitic changes [6]. These are usually reported MRI brain findings before IVLBCL is highly suspected as seen in our case. In a series of IVLBCL patients with CNS disease from Massachusetts General Hospital, it was found that six out of seven patients demonstrated CSF lymphocytosis, while only one of them had malignant cells in CSF cytology. Bone marrow infiltration has been reported in 38% of cases, and 5% of cases had circulating neoplastic cells on the peripheral blood smear [7]. Our patient has IVLBCL of CNS with bone marrow infiltration without showing abnormal blasts on PBF.

The clinical course of IVLBCL has been shown to be hostile and the prognoses of most cases are poor [8]. Data

in the literature indicate that anthracycline-based regimens, such as Rituximab and R-CHOP, are the treatment of choice [8]. It also has been found that patients with IVLBCL within the CNS are unlikely to respond to R-CHOP attributed to its poor penetration of the blood-brain barrier, and they should be treated with regimens similar to those used in primary CNS lymphoma in which intrathecal or high-dose systemic methotrexate should be included [9]. Without treatment, the 1-year mortality rate is approaching 80%, while its average survival rate is about 1 year [10].

Conclusion

The unpredictable clinical manifestation and the lack of diagnostic protocols available have resulted in the post-mortem diagnosis of IVLBCL. Most of the antemortem diagnoses of IVLBCL are made incidentally in biopsies performed for different reasons. We should always have a low threshold to biopsy abnormal brain or skin lesions in order to speed up the diagnosis process.

What is new?

There were case reports published on CNS lymphoma previously; however, this case report highlights the rare presentation of IVLBCL with CNS manifestations and challenges to reach the definitive diagnosis.

List of Abbreviations

ANA	Antinuclear antibody
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
EEG	Electroencephalogram
GCB	Germinal center B-cell
IVL	Intravascular lymphoma
IVLBCL	Intravascular large B-cell lymphoma
LDH	Lactate dehydrogenase
MRI	Magnetic resonance imaging

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this case report.

Funding

None.

Consent for publication

The patient has given informed, written consent for the publication of this case report in a medical journal.

Summary of the case

1	Patient (gender, age)	Female, 49 years old
2	Final diagnosis	CNS IVLBCL with marrow infiltration
3	Symptoms	Altered behaviors and seizures
4	Medications	RCHOP, levetiracetam, and sodium valproate
5	Clinical procedure	Lumbar puncture, bone marrow aspirations, and trephine biopsy
6	Specialty	Neurology and hematology

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Author details

Shu Ann Hon¹, Jie Siang See¹, Jack Son Wee¹, Yu Jin Tee², Efram Jamian³, Hamdi Achok¹, Soo Min Lim¹

1. Department of Internal Medicine, Hospital Sultanah Aminah, Johor Bahru, Malaysia
2. Department of Radiology, Hospital Sultanah Aminah, Johor Bahru, Malaysia
3. Department of Pathology, Hospital Sultanah Aminah, Johor Bahru, Malaysia

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