Case Report

Atypical Presentation and Aggressive Evolution of Primary CNS Lymphoma (PCNSL)

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Abstract

Patients with Primary CNS Lymphoma (PCNSL) typically present with focal neurological deficits with neuroimaging showing a solitary, non-haemorrhagic mass. We describe a 48-year-old-woman who presented with her first lifetime seizure with no enhancing intracranial mass, who 7 months later, developed focal deficits and was found to have multifocal enhancing lesions associated with intracerebral haemorrhage, which on biopsy were consistent with a PCNSL. This case highlights several atypical aspects of PCNSL, from its presentation with GTCS as seen in about 14% cases, to the atypical MRI finding of non-enhancing bi-temporal lobe hyperintensities at presentation with the subsequent evolution of multifocal haemorrhagic lesions. It also highlights the emerging genetic and molecular diagnostic markers in serum and CSF, while underscoring the importance of appropriately timing CSF evaluation for an accurate and reliable cytometric analysis. We also review the relevant literature on the imaging characteristics of PCNSL. Finally, it reviews some of the atypical cases of PCNSL published in the English literature and adds to that list as an aggressive symptomatic PCNSL that presented without an enhancing-intracranial mass-lesion, with the subsequent development of multifocal lesions associated with an intraparenchymal haemorrhage.

Keywords: CNS lymphoma, PCNSL, MRI, Intraparenchymal haemorrhage

Introduction:

Primary CNS Lymphoma represents about 4% of newly diagnosed primary brain tumours [1]. The incidence peaked in the mid-1990's and was largely driven by the HIV/AIDS pandemic, with age-standardized incidence rates having increased from 0.30/100, 000 persons (1989–1995) to 0.44/100, 000 persons (2009–2015), with the largest incidence increase in the age-groups 61–70 and >70 years [2]. Most cases of PCNSL in immunocompetent hosts occur in their fifth decade distributed equally between men and women [3]. Nearly 85% of them are aggressive Diffuse Large B-Cell Lymphomas (DLBCL). They most commonly present with focal neurological deficits but about 14% will present with seizures [3]. A diagnosis of PCNSL can be considered with a positive cytology obviating the need for a biopsy, however suffers from low and variable sensitivity [4]. MRI brain at presentation is almost always abnormal and typically shows a solitary, non-haemorrhagic mass that demonstrates restricted-diffusion and typically will be situated in the deep, peri-ventricular white matter [5]. Blood products and calcifications are rare findings for a PCNSL even on high-resolution susceptibility weighted imaging (SWI) which relates to it's poor vascularity, differentiating it from malignant gliomas and metastases [6]. Treatment has evolved from radiotherapy in 1960's to chemoimmunotherapy with rituximab in 2000's [7]. Untreated PCNSL can be

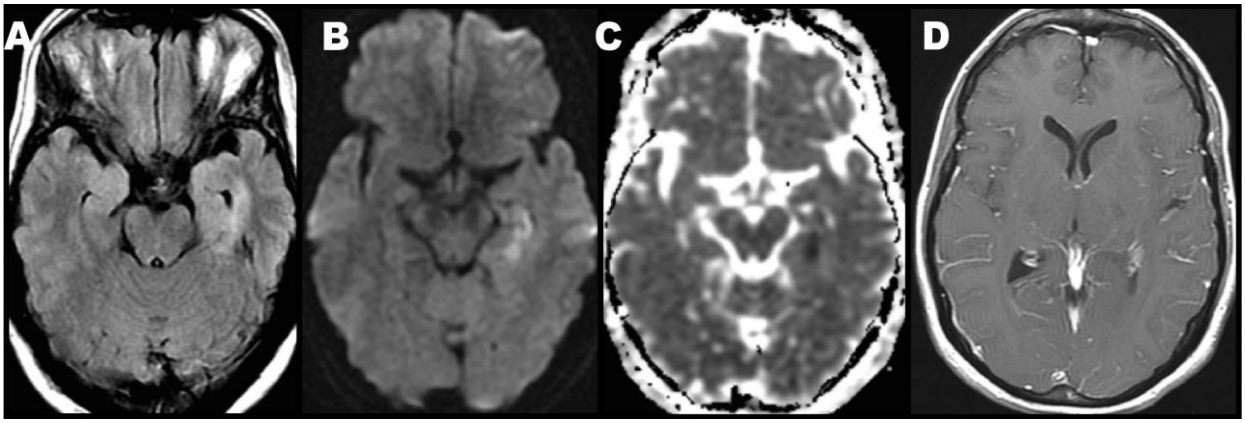

Figure 1. MRI brain on presentation: Axial T2 FLAIR (A) showing bilateral medial temporal hyperintensities, greater on the left with restricted diffusion of the left hippocampus (B and C). T1 post-contrast image shows no evidence of meningeal or parenchymal pathology.

rapidly fatal with an approximate survival of 1.5 months from diagnosis, while with treatment the overall 5-year survival in immunocompetent adults is about 30% [2]

Case:

A 48-year-old healthy Caucasian woman initially presented to our institution after a two-minute witnessed generalized tonic-clonic seizure (GTCS) while at work. Emergency medical personnel on arrival found her to be confused and constantly picking at her clothes. This was followed by another witnessed GTCS in the emergency room lasting about 45 seconds, about an hour after the first GTCS. She had been in her usual state of health up-until her first seizure without any prior prodromal or constitutional symptoms and specifically denied any sub-acute cognitive-behavioural changes or headaches, hours-to-days preceding her first GTCS. Neurologic examination showed poor short-term recall without any lateralizing signs. She was afebrile with a white cell count of 17, 000/µL. Contrast enhanced brain MRI (Figure: 1) showed non-enhancing bi-temporal hyperintensities. Such a presentation introduced a broad differential diagnosis as discussed below, of which HSV encephalitis was most concerning. IV acyclovir (10mg/kg every 8 hours) was started along with IV levetiracetam (750mg every 12 hours). IV dexamethasone (8mg every 8 hours) was added for their adjunctive role in HSV encephalitis as well as for a potential benefit if this was in-fact autoimmune encephalitis. Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis with 9 nucleated cells/Cu mm (95% lymphocytes) and an unremarkable infectious panel including HSV I/II polymerase chain reaction (PCR) (Table: 1). Acyclovir was subsequently discontinued. Though autoimmune encephalitis was initially considered, the patient did not meet the diagnostic criteria for such (as described below) and thus steroids were discontinued after the first 48 hours. A CT scan of the chest, abdomen and pelvis showed a thyroid mass that was benign on biopsy. A final diagnosis could not be reached and since she had returned to her neurological baseline, the patient was scheduled for an interval MRI-brain-with-contrast 4 weeks from presentation to monitor the evolution of her bi-temporal lesions. In the interim a complete serum and CSF autoimmune and paraneoplastic panel returned negative (Table: 1). Unfortunately, the patient never followed-up as scheduled. She returned back to her baseline and resumed work as a chef. Over the next 6 months she experienced a progressive cognitive decline and could 'no longer remember her recipes' but did not report these to the clinic until seven months from her initial discharge, when she presented with confusion and left sided weakness. Repeat MRI brain (Figure: 2) now showed a large enhancing basal ganglia lesion (2.8 x 2.5 x 2.8 cm) with punctate foci of enhancement in right thalamus and caudate with an additional ipsilateral enhancing parietal lobe lesion and a contralateral FLAIR hyperintense but non-enhancing inferior frontal lesion. An uncharacteristic intraparenchymal haemorrhage was also noted.

Table: 1 Laboratory Investigations at initial Presentation (Prior to steroid administration)

Source	*Parameter*	*Result*
Blood	White cell count	17, 000/ µL
	Differential	93% Neutrophils, 4% lymphocytes, 2.3% monocytes, 0% eosinophils and 0.1% basophils
	Platelet count	312, 000/µL
	Basic Metabolic Profile	Sodium 140 mmol/L, Potassium 3.7 mmol/L, Creatinine 1.6 mg/dL, glucose 187 mg/dL, calcium 9.9 mg/dL
	Liver Function tests	Aspartate aminotransferase 42 IU/L, Alanine aminotransferase 33 IU/L, Total bilirubin 0.2 mg/dL, Alkaline phosphatase 50 IU/L
	Creatine Kinase	487 U/L
	Erythrocyte sedimentation rate	5 mm/hour
	C-Reactive protein	1.32 mg/dL
	GAD-65 Antibody	<5 IU/mL
	Infectious panel	Following tested negative: CMV DNA RT-PCR, EBV DNA PCR, HIV1/2 antibody Screen, HSC I/II RT-PCR, Syphilis MIA <0.2 AI, Hepatitis panel
CSF	Routine (tube 4)	Nucleated cells: 9/Cu. mm (95% lymphocytes, 6% monocytes), RBC 3/Cu. mm, Protein 37 mg/dL, Glucose 70 mg/dL
	Gram stain and culture	No neutrophils, no bacteria, no growth
	Cytology and flow-cytometry	Ordered, but could not be processed until 48-hours post-collection rendering the sample un-evaluable
	Autoimmune Encephalitis panel	Following tested negative: NMDA-R Ab; VGKC Cplx Ab, GAD 65 Ab assay; GABA-B-R Ab; AMPA-R Ab, ANNA -1 Ab, ANNA -2 Ab, ANNA -3 Ab, AGNA-1 Ab, PCA-1 Ab, PCA-2 Ab, PCA-Tr Ab, Ampiphysin Ab, CRMP-5 –IgG Ab
	Infectious disease panel	VDRL, Herpes Simplex virus I/II PCR, West Nile virus IgM/IgG Ab

However, the initially observed bi-temporal T2/FLAIR hyperintensities had completely resolved. Flow-cytometric and immunohistochemical (IHC) analysis of the right parietal lesion established the diagnosis of a DLBCL (Figure: 3) with the absence of systemic involvement on PET scan suggesting a PCNSL. Epstein-Barr virus serology was negative. She was started on the MATRix regimen with re-staging scans after four months of treatment showing a partial radiographic response (Figure: 2H & I).

Discussion:

We present a case of PCNSL with an atypical presentation and an aggressive course associated with intracerebral haemorrhage.

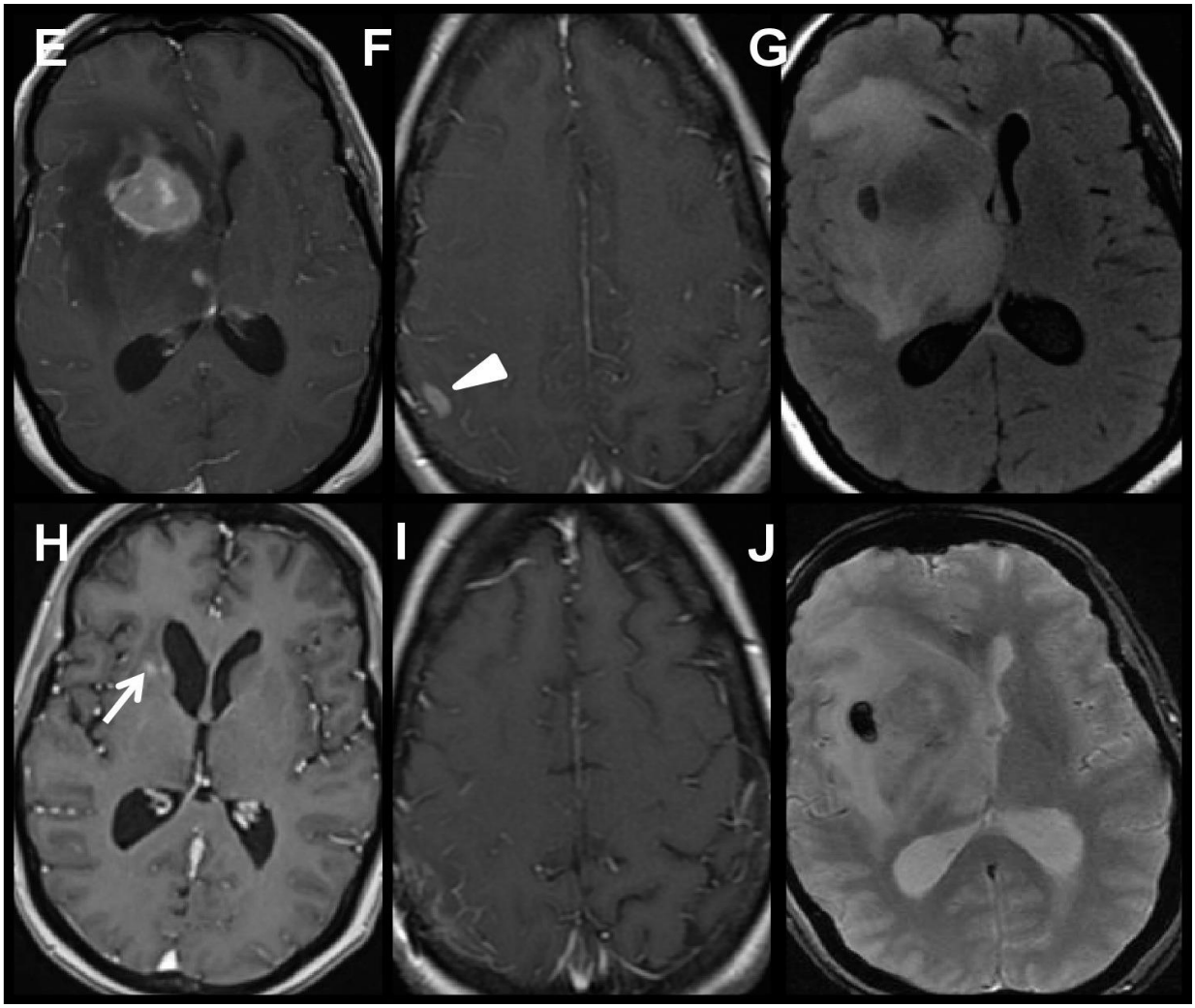

Figure 2. MRI brain seven months from initial presentation showing a large enhancing basal ganglia lesion (2.8 x 2.5 x 2.8 cm) with punctate foci of enhancement in right thalamus and caudate (E) connected to the basal ganglia lesion by FLAIR hyperintensity (G). There was also a superior ipsilateral enhancing parietal lobe lesion (F) and a contralateral FLAIR hyperintense non-enhancing left inferior frontal lesion. An uncharacteristic hemorrhage within the tumor bed is seen on gradient ECHO sequence (J). Partial response seen at 4 months after initiation of chemotherapy (H, I) with persistent contrast enhancement (arrow)

Firstly, the bi-temporal hyperintensities on MRI brain which carry a wide differential diagnosis from infectious encephalitis and neoplastic infiltration to autoimmune/paraneoplastic limbic encephalitis and post-ictal change. Several infections can present with such bi-temporal hyperintensities specifically HSV-I/II, HHV-6, CMV and neurosyphilis [8]. While HSV can cause an acute encephalitis in immunocompetent patients, HHV-6 encephalitis typically occurs 2-3 weeks after a solid-organ or bone-marrow transplant [8]. This prompted the initiation of IV acyclovir on admission which was discontinued when the PCR for HSV returned negative. While HHV-6 PCR was not tested, it is unlikely that the patient had an infectious encephalitis given that she remained afebrile with quick resolution of her leucocytosis and had a rapid improvement to baseline neurological function within 24-48 hours of presentation. Although autoimmune Limbic Encephalitis (LE) was considered initially as she had met three of four diagnostic criteria for a *definite* diagnosis [9], the lack of a subacute cognitive-behavioural prodrome prior to her sudden-onset-GTCS and the presence of

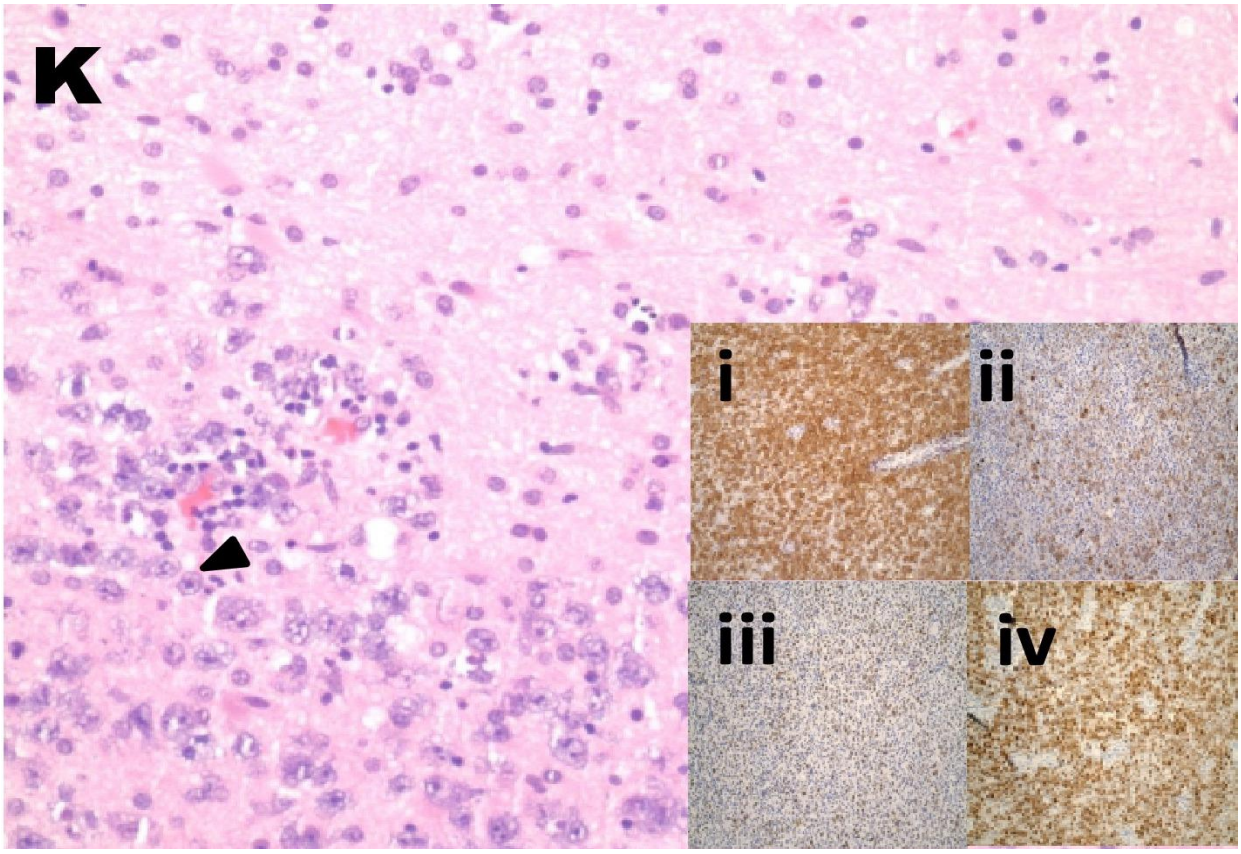

Figure 3. Hematoxylin and eosin stain (K) showing angiocentric infiltration of pleomorphic (arrowhead) lymphocytes invading the brain parenchyma, which were positive for CD20 (i), CD10 (ii), BCL-6 (iii) and MUM-1 (iv) markers

diffusion-restriction on MRI brain made it a less likely aetiology. Subsequently, the patients steroids were discontinued 48 hours from initiation, with a plan to track the evolution of the underlining pathology with an interval 4-week-MRI-brain. While paraneoplastic LE remains another possible differential, its occurrence in non-Hodgkin lymphomas is exceedingly rare with only a handful of cases reported, none with PCNSL [10]. In a review-series of 137 paraneoplastic limbic encephalitis cases in the English literature, not a single case was attributable to PCNSL [11]. However, they described one patient with cognitive dysfunction and bi-temporal T2-weighted abnormalities with the subsequent development of basal ganglia lesions proven to be PCNSL on biopsy [11]. Lymphomas may cause similar MRI changes and tend to be exquisitely sensitive to steroids, but the initial MRI brain was performed before steroid-initiation and the patient had not been on any form of steroid therapy prior to her first GTCS. While non-enhancing PCNSL cases have been described in immunocompetent patients, their estimated frequency is <1% [12]. Our patient's bi-temporal lesions were non-enhancing, unlike all of the 102-PCNSL cases in a Norwegian series [13]. Finally, the lympholytic effect of steroids is almost-always transient and thus the complete resolution (in the absence of any treatment) of those bi-temporal hyperintensities at the time of her relapse, along with their non-enhancing nature argues against them as having represented an early CNS lymphoma. Post-ictal changes on T2/FLAIR sequences can infrequently be associated with corresponding diffusion-restriction; with higher percentage drops in ADC signal being associated with subsequent sclerotic change and partial epilepsy [14]. Thus with the lack of an obvious infectious aetiology, inability to identify a central or systemic neoplastic aetiology and the rarity of paraneoplastic LE in PCNSL, we planned to refrain

Table 2. PCNSL cases with atypical presentation

No.	*Ref.*	*Immune status*	*Treatment with steroids*	*Duration of remissions (months)*	*Characteristic features*
1	31	IC	Y (all patients)	7-11	First description of remitting lesions in PCNSL, termed "Sentinel Lesions".
2	32	NA	N	1	Spontaneous resolution of multifocal lesions.
3	33	NA	Y, N	3	Steroid induced and spontaneous remissions in the same patient.
4	34	IC	N (1of 3 patients received steroids)	12-48	Longer remissions than previously described.
5	35	IC	N	1-11	Multiple spontaneous remissions with lesions migrating from right midbrain, to left thalamus, to a butterfly lesion.
6	36	NA	N (2 of 4 patients received steroids)	7-45	Spontaneous resolution in 2 of 4 cases.
7	37	NA	N	12	Systemic involvement at relapse treated with steroids and chemotherapy.
8	38	IC	N	12	Spontaneous remission in leptomeningeal disease.
9	39	IC	Y	NA	Bilateral infiltrating lesions in both hippocampi presenting with cognitive decline.
10	40	IC	Y	Died	Infiltrating brainstem DLBCL (biopsy proven), mimicking ocular Myasthenia Gravis (pyridostigmine responsive).

from any further steroid or immunosuppressant therapy until a follow up 4-week-MRI-brain, especially given that the patient had returned to her neurological baseline. In retrospect a hypothesis can be made for early microscopic tumor infiltration as the cause of her initial GTCS with the bi-temporal hyperintensities representing post-ictal change. Alternatively, it is possible that the temporal lobe hyperintensities were a manifestation of a rare paraneoplastic LE with frank lesions showing only months later.

Secondly, while PCNSL has been commonly implicated in producing "vanishing tumours" of the CNS [15], most of these cases have been treated with steroids. However, a few cases have regressed spontaneously without any use of corticosteroids (Table: 2). To establish a diagnosis of PCNSL cytology and flow cytometry can obviate the need for a biopsy, however suffers from low and variable sensitivity from 2%-32%, which likely reflects the differences in the populations studied as well as the CSF volume, handling, processing-time and interpretation [4]. This can be improved with larger volumes (≥10.5 mL) and repeat evaluations [17]. In a retrospective analysis of 219 patients with known hematologic malignancy, about 80% had a positive cytology or flow cytometry in the first sample drawn, with 25% positive for both [18]. Unfortunately in our patient the CSF sample drawn at initial admission could not be processed for cytology and flow cytometry until 48 hours later at which point it was rendered un-evaluable. Glantz et al. have reported a

36% false-negative-error rate when CSF cytology is delayed by 48 hours from collection [17]. Subsequently, a repeat CSF analysis was not performed as the patient had already received 48-hours of corticosteroids which are known to induce cytolysis and further reduce the sensitivity of cytology [4]. Additionally, the detection of a clonal B-cell population does not differentiate between lymphoma entities and may even be seen with non-malignant conditions [19]. Recently, promising advances have been made in the identification of serum and CSF diagnostic markers for CNS lymphoma, with a recent systematic-descriptive-analysis identifying CSF Cytokines (CXCL-13, interleukin-10 and neopterin) and MHC-proteins (beta-2-microglobulin) as having the greatest potential [20]. Baraniskin et al. employed a combination of microRNAs (miRNAs – *miR-21*, *miR-19b*, and *miR-92a*) in the CSF of patients with PCNSL using RT-PCR assays and found a significant specificity (96.7%) and sensitivity (95.7%) to differentiate PCNSL from other neurological conditions, specifically inflammatory diseases [21]. Finally, molecular analysis has become another armamentarium in the diagnosis of PCNSL with more than 70 aberrant genes reported in literature. A recent review identified 10 genes reported in >= 3 studies and found that half of them were implicated in the nuclear factor-κB (NF-κB) pathway (*CARD11, CD79B, MYD88, TBL1XR1 and TNFAIP3*) [19]. Of these, *CD79B* and *MYD88* are of specific interest, since they become mediators of the Bruton-tyrosine-kinase (BTK) pathway, irreversibly inhibited by Ibrutinib [22]. These markers would be extremely valuable in increasing the sensitivity and specificity of CSF analysis in diagnosing CNS lymphoma but have not yet been deployed in routine clinical practice and brain biopsy remains the gold standard despite a reported complication rate of ~ 8.5% (hemorrhage, seizures, infections) with ~ 1% mortality rate [19]. Tissue analysis showing angiocentric infiltration of large immunoblasts positive for germinal-centre (GC) *(CD10, bcl-6)* or late-GC *(MUM-1)* markers but negative for plasma cell markers *(CD-138)* makes the definitive diagnosis [16]. In our patient, the right parietal lesion was biopsied at the time of her second admission and showed a diffuse perivascular monomorphous infiltrate of atypical large lymphoid cells with pleomorphic nuclei and scant cytoplasm. Flow-cytometry showed expression of *CD45, CD19* and *CD20*. IHC studies showed large lymphoid cells, diffusely positive for the B-cell antigens such as *CD20*, *Pax-5*, *bcl-2*, *bcl-6* and *MUM-1* and negative for the plasma cell marker (*CD138),* Mantle cell lymphoma markers (*cyclin D1, SOX-11*) and large B cell lymphoma from multicentric Castleman disease (*HHV-8*). An in-situ hybridization study for Epstein-Barr encoding region (EBER) was negative. Fluorescent in-situ hybridization (FISH) of the parietal lesion detected the presence of *bcl-6* gene rearrangement in 93.5% nuclei, without any significant *bcl-2* or *C-myc* gene rearrangements. The cell proliferation antigen, *Ki-67* (MIB-1), was positive in greater than 90% of cells. Taken together, these findings led to the diagnosis of DLBCL in our patient.

Within 4-weeks of initial discharge she started developing cognitive decline, headaches and eventually focal neurodeficits, which are the presenting symptoms in 43%, 33% and 70% respectively [3]. Most PCNSL lesions are solitary with homogenous contrast enhancement as opposed to our patient who had heterogenous multifocal enhancement seen in 20-40%, with cerebral hemispheres (38%) and basal ganglia/thalamus (16%) being the most frequent locations, with the latter also being a poor prognosticator [24]. These imaging features are more reminiscent of PCNSL in immunocompromised patients (Table: 4). The high cellularity of PCNSL causes more restricted diffusion when compared to gliomas and metastasis, with lower ADC values predictive of a shorter progression-free survival [5]. Blood products and calcifications are rare findings for a PCNSL even on high-resolution susceptibility-weighted-imaging (SWI) which relates to it's poor vascularity [6]. Intraparenchymal haemorrhage is rare in PCNSL and was present in 2 of 21 (9.5%) immunocompetent patients with PCNSL in a Jordanian case series [25]. Another study based of the Norwegian cancer registry found a 8% prevalence (6/75 immunocompetent patients with PCNSL) of a concomitant intra-tumoral haemorrhage, one of whom had a tumor in a large chronic subdural hematoma [12]. This was slightly higher than the 2 % rate observed in a population-based study from the Alberta Cancer registry [26]. On CT-perfusion they show lower relative cerebral blood volume when compared with more vascular tumors such as high-grade gliomas and metastases. Punctate intra-tumoral susceptibility signal on thin-slice-SWI (1mm, 1.2mm) [6] and intra-tumoral blood-vessel-number

Table 3. Differences between AIDS and non-AIDS related cases of PCNSL

	Non-AIDS related PCNSL	*AIDS-PCNSL*
Incidence	4 per million people per year [1]	2 – 6 % (at least 1000 times higher than in the general population). Found to be as high as 10 % in autopsy series [41]
Clinical features	Mental status changes with elevated intracranial pressure (ICP) is seen in 35% and 32% cases respectively	Up to 50% and 14% cases can present with altered mental status and raised ICP [42]
Association with EBV	EBV genomic DNA is not present in majority of the tumors	EBV has a more central role in the pathobiology, with the probability of PCNSL increasing from 74% to more than 96%, when AIDS patients with mass-effect-causing- CNS lesions, show seronegativity to toxoplasma and test positive for EBV DNA [43]
Imaging	MRI brain shows homogeneous contrast enhancement in ~90% cases. Ring enhancement is rare, seen in 0%-13% cases.	Most cases show irregular contrast enhancement, with ring enhancement in up to 75% cases [5]

on SWI [27] are emerging measure to identify PCNSL. Over the years, therapy evolved from radiation only in the 1960's, to methotrexate-based chemotherapeutic regimens in the 1970's to chemoimmunotherapy with the addition of rituximab in the 2000's [7]. A recent randomized phase 2 trial by the IELSG32 group identified the MATRix regimen, used in our patient, as a new promising standard of care with a 49% rate of complete response (CR) and 37% rate of partial response (PR) [28]. One of the most important limitations of systemic chemotherapy is the delivery of agents across the blood-brain-barrier (BBB). Thiotepa (an alkylating agent) can cross the BBB freely with a plasma-CSF ratio of 100% [28], but rituximab which is an anti-CD-20 monoclonal antibody (mAb) penetrates the CSF at much lower concentrations (0.1% to 4.4%) after IV administration [29]. However, contrast-enhancing lesions indicate disruption of the BBB which would allow such bulky mAb's to exert their effect on CNS lymphoma even when used as monotherapy, thus validating their incorporation in systemic immunochemotherapy for this disease [23]. MTX on the other hand, despite having a lower permeability across the BBB (approximately 5% of plasma levels) can be delivered at relatively high doses [28]. Subsequently, newer studies are looking at intrathecal administration of immunochemotherapy with some evidence for increased CR rates [29]. Alternatively, others have attempted osmotic BBB disruption with subsequent use of IA MTX based chemotherapy with outcomes comparable or superior to other PCNSL treatment regimens [30]. Our patient had a significant lesion burden with a PR to the MATRix regimen which in part can be hypothesized to have been facilitated by the enhanced penetration of rituximab into the CSF from a compromised BBB. Finally, patients with relapsed or refractory (r/r) CNS lymphoma respond poorly to traditional regimens, with a recent single-centre, dose-escalation trial in 20 patients with r/r CNS lymphoma treated with Ibrutinib demonstrating remarkable single agent activity. It causes irreversible inhibition of BTK, a cytoplasmic protein expressed on B-lymphocytes but absent in the plasma cells and T cells. 5 of 13 r/r PCNSL and 4 of 7 r/r SCNSL cases demonstrated a CR with another 5

Table 4. PCNSL cases with reported intraparenchymal haemorrhage from major English literature case-reports

No.	*Ref.*	*age/sex*	*Type*	*Clinical presentation*	*PCNSL location*	*HIV*
1	44	29/M	NA	Headache, oral dyskinesia	Lt. F and P	(+)
2	45	55/M	DLBCL	GTCS	Lt. F	(-)
3	46	49/F	DLBCL	Acute encephalopathy	Lt. F	N/A
4	47	57/F	DLBCL	Rt. Arm weakness and dsyarthria	Lt. F and Rt. P	(-)
5	48	67/M	DLBCL	Vision loss	Lt. F	(-)
6	25	55/M	NA	NA	HWM	(-)
7	25	45/M	NA	NA	Periventricular	(-)
8	Our patient	48/F	DLBCL	Lt face, arm, leg weakness	Rt. F	(-)
9-14	13	6 of 75 cases of immunocompetent patients described by Haldorsen et al. from the Norwegian Cancer Registry (1989-2003)				
15-18	6	4 of 19 immunocompetent patients described by Sakata et al.				
19	26	1 of 50 cases of immunocompetent patients described by Hao et al. from the Alberta cancer registry (1975-1996)				
20, 21	49	2 of 37 cases of immunocompetent patients described by Coulon et al.				
22-25	50	4 of 19 cases described by Ueda et al.				
26-28	51	3 of 54 immunocompetent patients described by Malikova et al.				
29-31	52	3 of 7 cases of T-cell PCNSL in immunocompetent patients described by Kim et al.				

patients with r/r PCNSL demonstrating a PR [22]. The prognosis of PCNSL continues to improve with the 5-year relative-survival for patients aged 18-60 years and 61-70 years, improving from 22 to 56% and from 13 to 35% respectively, between the calendar periods 1989–1995 and 2009–2015 [2].

Conclusion:

PCNSL is an aggressive disease, especially when untreated and its occurrence in non-eloquent areas, as seen in our patient, can delay diagnosis by several months. CSF cytomorphic-cytometric analysis should be performed immediately, as despite the several advances made in CSF molecular diagnostics, they still remain a key tool for the early identification of a potential intrathecal neoplastic process with their sensitivity dramatically reducing with time. Seizures as a presenting symptom for PCNSL is seen in only 14% of the cases. Upon presentation they almost always have enhancing parenchymal lesions, however as seen with our case they can also present without such lesions and therefore one must ensure a close clinico-radiographic follow-up for patients who develop suspicious neurologic symptoms (e.g. seizure) without a clear aetiology. Finally, multifocal PCNSL is less common in immunocompetent patients but can be seen in up to 35% of the cases while associated intratumoral haemorrhage is even rarer, seen in 2%-9.5% of PCNSL cases. We conclude with the hypothesis of post-ictal change from microscopic tumor infiltration or an extremely rare paraneoplastic limbic encephalitis as the cause of our patients initial bi-temporal lesions.

Abbreviations:
AGE, advanced glycation end product
BBB, blood brain barrier
DLBCL= diffuse large B cell lymphoma
CMV, cytomegalo virus
CR, complete response
CXCL, c-x-c motif ligand
EBV= epstein barr virus
GTCS, generalized tonic-conic seizure
HSV, herpes simplex virus
HHV, human herpes virus
HWM, hemispheric white-matter
IELSG, International Extranodal Lymphoma Study Group
IA, intraarterial, IC, immunocompetent
IL, interleukin
IV, intravenous
Lt., left
Rt., right
mAb, monoclonal antibody
MATRix, methotrexate, cytarabine, thiotepa and rituximab
MHC, major histocompatibility complex
MRI, magnetic resonance imaging
N, no
NA, not available
PCR, polymerase chain reaction
PCNSL, primary CNS lymphoma
PET, positron emission tomography
PR, partial response
SCNSL, secondary CNS lymphoma
Y, yes

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