

# A challenging case of EBV-positive CNS lymphoma in a multiple sclerosis patient: case report and systematic review of the literature

Lucia Campetella<sup>1</sup>, Anna Chiara Landi<sup>1</sup>, Gabriele Lucioni<sup>1</sup>, Vittorio Riso<sup>1</sup>, Marisa Distefano<sup>1</sup>, Elisa Iacovelli<sup>1</sup>, Sandro Misciagna<sup>1</sup>, Alessandro Valenza<sup>1</sup>, Daniele Mei<sup>1</sup>, Daniele Marruzzo<sup>2</sup>, Marcella Masciullo<sup>1</sup>, Nicola Pio Falcone<sup>1</sup>

1. UOC Neurologia, Ospedale Santa Rosa, Viterbo (VT)  
2. UOC Neurochirurgia, Ospedale Santa Rosa, Viterbo (VT)

## OBJECTIVES

- Primary central nervous system lymphoma (PCNSL) is a rare brain neoplasm occurring mostly in immunocompromised patients.
- Herein, we report a case of Epstein-Barr virus (EBV)-positive PCNSL in an immunocompromised multiple sclerosis (MS) patient and identify additional cases.

## MATERIALS AND METHODS

- Case report illustrating a patient admitted to our Neurology unit and systematic review of the literature investigating additional cases of PCNSL in MS patients.
- The systematic review of the literature was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Two reviewers (LC and ACL) independently searched MEDLINE/PubMed and Web of Science using the search term "multiple sclerosis" combined with one of the following terms: "primary CNS lymphoma", "CNS lymphoma", "EBV lymphoma" and "lymphoma".

## RESULTS

- A 64-year-old woman developed slowly progressive right-side hemiparesis and speech impairment in October 2024. She had been receiving azathioprine since MS diagnosis 21 years prior and her MS was non-active and non-progressive.
- Brain MRI showed multiple confluent T2 hyperintense white matter lesions in the left parietal lobe with contrast enhancement (Figure 1); cerebrospinal fluid analysis was normal except for hyperproteinorachia. Intravenous methylprednisolone was administered with almost complete recovery.
- One week later the patient presented generalized seizures and worsening of hemiparesis and developed super-refractory status epilepticus. Brain biopsy was performed, and pathology revealed an EBV-positive diffuse large B cell lymphoma. Rituximab was initiated leading to substantial neurological recovery.

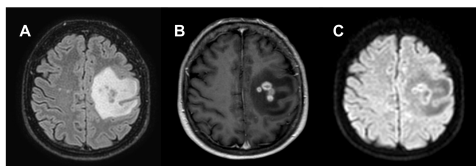


FIGURE 1. MRI findings. A) FLAIR sequences depicting confluent nodular T2 hyperintensities in the left parietal lobe with surrounding edema and mass effect. B) Lesions showed ring-like contrast enhancement and C) peripheral restricted diffusion with incomplete ring appearance.

Abbreviations: DWI, diffusion weighted imaging; FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging.

- From a systematic review of the literature, 10 additional cases of PCNSL in MS patients were identified (Table 1). Median age at PCNSL diagnosis was 45.5 years (range 28-61, IQR 40-55).
- Eight patients were actively undergoing treatment with natalizumab (3/8, 38%), fingolimod (2/8, 25%), interferon/glatiramer acetate (2/8, 25%), and azathioprine (1/8, 12%). EBV was detected in the tumor tissue of two patients.

Ref	Sex, age (MS duration)	DMT at diagnosis	Clinical presentation	MRI findings	Histological diagnosis
1	M, 55 (5)	FGL for 4 years	Blurred vision, headache	Location: Right parietal lobe Mass effect: +, edema: - CE: + (ring-like), DWI: + (ring-like)	Diffuse large B-cell lymphoma (DLBCL) [EBV+] DLBCL
2	F, 51 (24)	FGL for 14 months	Right side hemiparesis, aphasia	Location: Left frontal lobe Mass effect: +, edema: + CE: + (homogeneous), DWI: -	DLBCL
3	F, 61 (35)	IFN $\beta$ -1a for 10 years	Right third cranial nerve palsy, left side hemiparesis	Location: Right thalamus, midbrain, pons Mass effect: +, edema: + CE: + (homogeneous), DWI: +	DLBCL
4	M, 47 (23)	AZA for 20 years	Headache, vertigo	Location: Multiple cerebellar lesions Mass effect: +, edema: + CE: +, DWI: NA	Classic Hodgkin's lymphoma [EBV+]
5	M, 28 (5)	NTZ for 7 months	Confusion, left arm weakness	Location: Right frontal lobe Mass effect: +, edema: + CE: +, DWI: NA	DLBCL [EBV-]
6	F, 44 (4)	NTZ for 3 months	Cognitive impairment, staxia, left lower limb weakness	Location: Right temporal lobe Mass effect: +, edema: + CE: + (weak), DWI: NA	DLBCL [EBV-]
7	M, 40 (20)	None - after onset	Blurred vision, headache, cognitive disturbances	Location: Multiple lesions in brainstem and splenium Mass effect: +, edema: + CE: +, DWI: NA	B-cell lymphoma intermediate between DLCL and Burkitt [EBV-]
8	M, 55 (2)	IFN $\beta$ -1a plus GA for 1 year	Acute cognitive and behavioural disturbances	Location: Large lesion involving both frontal lobes and corpus callosum Mass effect: +, edema: + CE: +, DWI: NA	DLBCL
9	M, 40 (3)	NTZ for 21 months	Right-sided hypoesthesia	Location: Large lesion left corona radiata + two lesions right frontal cortex Mass effect: +, edema: + CE: +, DWI: NA	B-cell lymphoma intermediate between DLCL and Burkitt [EBV-]
10	M, 32 (5)	None	Seizures, altered consciousness, tetraparesis	Location: Multiple lesions in right hemisphere Mass effect: +, edema: + CE: + (ring-like), DWI: NA	Centroblastic variant of DLCL

TABLE 1. Clinical, radiological and diagnostic characteristics of the 10 patients identified from the systematic review. Age refers to age at lymphoma diagnosis.

Abbreviations: AZA, azathioprine; CE, contrast enhancement; DLBCL, diffuse large B-cell lymphoma; DMF, dimethyl fumarate; DMT, disease-modifying treatment; DWI, diffusion-weighted imaging; EBV, Epstein-Barr virus; FGL, fingolimod; GA, glatiramer acetate; IFN, interferon; NA, not available; NTZ, natalizumab.

## DISCUSSION AND CONCLUSIONS

- ✓ This is the third case of EBV-positive PCNSL reported so far among MS patients undergoing disease-modifying treatments.
- ✓ Atypical clinical symptoms and radiological findings in MS patients with long-standing stable disease should alert physicians for alternative diagnoses.
- ✓ Prompt recognition and treatment is crucial as untreated PCNSL leads to a rapidly fatal course.

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