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1 ***Progressive Multifocal Leukoencephalopathy after first line Radiotherapy and Temozolomide for***  
2 ***Glioblastoma***

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29 A 59-year-old woman was diagnosed with left fronto-temporo-occipital glioblastoma  
30 (**Figure1a**). After biopsy, she received two neo-adjuvant temozolomide cycles (TMZ, 150-200  
31 mg/m<sup>2</sup>) as radiotherapy was delayed due to emerging COVID pandemic. She eventually received  
32 standard chemoradiation (60 Gray in 30 fractions plus daily TMZ, 75 mg/m<sup>2</sup>, **Figure1b**). She received  
33 oral methylprednisolone (16 mg/day) for a short period before and during chemoradiation. Baseline  
34 lymphocyte count was 3694/μL. After chemoradiation, partial clinico-radiological improvement was  
35 noticed (**Figure1c**); Karnofsky performance status was 70, and her neurological examination mainly  
36 revealed a non-fluent aphasia.

37 Shortly after the second adjuvant TMZ cycle (200 mg/m<sup>2</sup>), her neurological status rapidly  
38 declined with behavioural disorders in the foreground. This contrasted with brain MRI, which  
39 illustrated signs of oncological response with reduction in both tumor infiltration and mass effect.  
40 Electroencephalography was did not show epileptic activity or typical encephalopathic patterns. An  
41 extensive screening, including hepatic, renal, and thyroid function, ammonia, copper, folates, and  
42 vitamin levels, HIV and syphilis serologies, was normal excepted for lymphopenia (770/μL) and  
43 moderately decreased vitamin B12 (132 pmol/L). CSF analysis displayed normal protein and glucose,  
44 one leucocyte per mm<sup>3</sup>, and was negative for herpesviruses by PCR. Intravenous B12  
45 supplementation was initiated.

46 The patient continued to deteriorate to a stuporous state, with a rapidly progressive left spastic  
47 hemiplegia, ipsilateral to the tumour. MRI was negative for tumor progression or cerebrovascular  
48 complications but showed a new hyperintense lesion involving the right internal capsule and the  
49 cortico-subcortical right frontal lobe on diffusion-weighted sequences, compatible with a  
50 demyelination front (**Figure1d**). This prompted repeated CSF analysis, which led to the identification  
51 of JC polyomavirus (JCV). A diagnosis of progressive multifocal leukoencephalopathy (PML) was  
52 established according to current criteria<sup>1</sup>. Lymphocyte immunophenotyping disclosed severe CD4+  
53 and B lymphocyte deficiency (50/μL and 43/μL, respectively). Temozolomide was definitively

54 discontinued. The patient was discharged to a rehabilitation unit and died two months after she was  
55 admitted for neurological deterioration.

56 Progressive multifocal leukoencephalopathy is a demyelinating disease of CNS caused by the  
57 reactivation of the ubiquitous JCV (present in a quiescent state in up to the 80% of the adult  
58 population) in conditions of profound immunosuppression, such as AIDS, haematological  
59 malignancies, or immunosuppressive treatments<sup>2</sup>. To our knowledge, this is the second description  
60 of PML in a glioma patient treated with TMZ. The first was a 60-year-old glioblastoma patient with  
61 a fatal, histologically proven, PML developed two years after dose-dense TMZ plus isotretinoin.<sup>3</sup> Our  
62 report is the first case of PML during standard adjuvant TMZ. Chronological relationship and the  
63 absence of other immunosuppression cause led us to consider the causative role of radiation therapy  
64 plus TMZ. Treatment with radiation and TMZ is known to induce severe, protracted lymphopenia in  
65 glioma patients, affecting preferentially the CD4<sup>+</sup> T-cell compartment<sup>4</sup>, and to a lesser extent B-cells,  
66 as in our patient. Other factors may impair CD4<sup>+</sup> cells function in glioblastoma patients, including  
67 glucocorticoids and the tumor itself. CD4<sup>+</sup> lymphopenia is the main risk factor for PML<sup>2</sup>.

68 It is plausible that some cases may have been underdiagnosed, as PML can mimic multifocal  
69 non-enhancing glioma progression. A prompt diagnosis may impact patients' management.  
70 Chemotherapy can be interrupted, although TMZ-induced lymphopenia may last for months<sup>4</sup>.  
71 Immune-checkpoint inhibitors, which were recently demonstrated to be effective in treating PML in  
72 selected patients<sup>5</sup>, could be also considered, although evidence of efficacy is lacking in this context.

73 In conclusion, neuro-oncologists should be aware of the rare but possible occurrence of PML  
74 in glioma patients with CD4<sup>+</sup> lymphopenia. The diagnosis should be considered in the occurrence of  
75 unexplained clinical worsening. Lymphocyte phenotyping including CD4<sup>+</sup> count could be useful  
76 during the regular follow-up to identify patients at higher risk to develop this serious complication.

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92 **FIGURE LEGEND**

93 **Figure1.** radiological evolution of the patient over time. **a:** at diagnosis, showing a diffusely  
94 infiltrating, non-enhancing IDH-wildtype glioblastoma in left temporoparietal lobes (top: T1-  
95 weighted, post-gadolinium [T1w-Gd] sequence; bottom: T2-weighted, FLuid Attenuated Inversion  
96 Recover [FLAIR] sequence). **b:** radiotherapy planning, showing irradiated brain volumes (circled:  
97 planning target volume) **c:** one month after the completion of concomitant chemoradiation,  
98 demonstrating a partial oncological response with reduced mass effect (top: T1w-Gd sequence;  
99 bottom: FLAIR sequence) **d:** one month after the onset of neurological deterioration, a novel  
100 hyperintense lesion involving the right internal capsule (dotted white arrow) and a less defined,  
101 cortico-subcortical hyperintensity (thick grey arrow), with an aspect compatible with a demyelination  
102 front, visible on diffusion-weighted sequences, without a corresponding post-gadolinium contrast  
103 enhancement (not shown).

