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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/m²) 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/m², **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/m²), 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 mm³, 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 criteria¹. 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 treatments². 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.³ 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⁺ T-cell compartment⁴, and to a lesser extent B-cells,
66 as in our patient. Other factors may impair CD4⁺ cells function in glioblastoma patients, including
67 glucocorticoids and the tumor itself. CD4⁺ lymphopenia is the main risk factor for PML².

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 months⁴.
71 Immune-checkpoint inhibitors, which were recently demonstrated to be effective in treating PML in
72 selected patients⁵, 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⁺ lymphopenia. The diagnosis should be considered in the occurrence of
75 unexplained clinical worsening. Lymphocyte phenotyping including CD4⁺ 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).

