Progressive multifocal leukoencephalopathy after first-line radiotherapy and temozolomide for glioblastoma

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Alberto Picca*[1], Clément Desjardins*[1], Kévin Bihan[2], Nicolas Weiss[3], Amélie Guihot[4], Lucia Nichelli[5], Loic Feuvret[6], Valérie Pourcher[7], Mehdi Touat[1], Caroline Dehais[1]

1. Service de Neurologie 2-Mazarin, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, AP-HP, Paris, France.
2. Centre Régional de Pharmacovigilance, Service de Pharmacologie, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, AP-HP, Paris, France.
3. Département de Neurologie, Unité de Médecine Intensive Réanimation Neurologique, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, AP-HP, Paris, France.
4. Centre d'Immunologie et des Maladies Infectieuses (CIMI-Paris), Département d'Immunologie, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, AP-HP, Paris, France.
5. Service de Neuroradiologie, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, AP-HP, Paris, France.
6. Service de Radiothérapie, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, AP-HP, Paris, France.
7. Service de Maladies Infectieuses et Tropicales, Hôpitaux Universitaires La Pitié Salpêtrière - Charles Foix, AP-HP, Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique, Paris, France.

* these authors contribute equally to the work

Corresponding author:

Dr Caroline Dehais

Service de Neurologie 2-Mazarin,

Groupe Hospitalier Pitié-Salpêtrière, AP-HP, 47 Boulevard de l'Hôpital, 75013, Paris, France

Telephone: +33142160435

E-mail: caroline.dehais@aphp.fr

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A 59-year-old woman was diagnosed with left fronto-temporo-occipital glioblastoma (**Figure1a**). After biopsy, she received two neo-adjuvant temozolomide cycles (TMZ, 150-200 mg/m²) as radiotherapy was delayed due to emerging COVID pandemic. She eventually received standard chemoradiation (60 Gray in 30 fractions plus daily TMZ, 75 mg/m^2, **Figure1b**). She received oral methylprednisolone (16 mg/day) for a short period before and during chemoradiation. Baseline lymphocyte count was 3694/µL. After chemoradiation, partial clinico-radiological improvement was noticed (**Figure1c**); Karnofsky performance status was 70, and her neurological examination mainly revealed a non-fluent aphasia.

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

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

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

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

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

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

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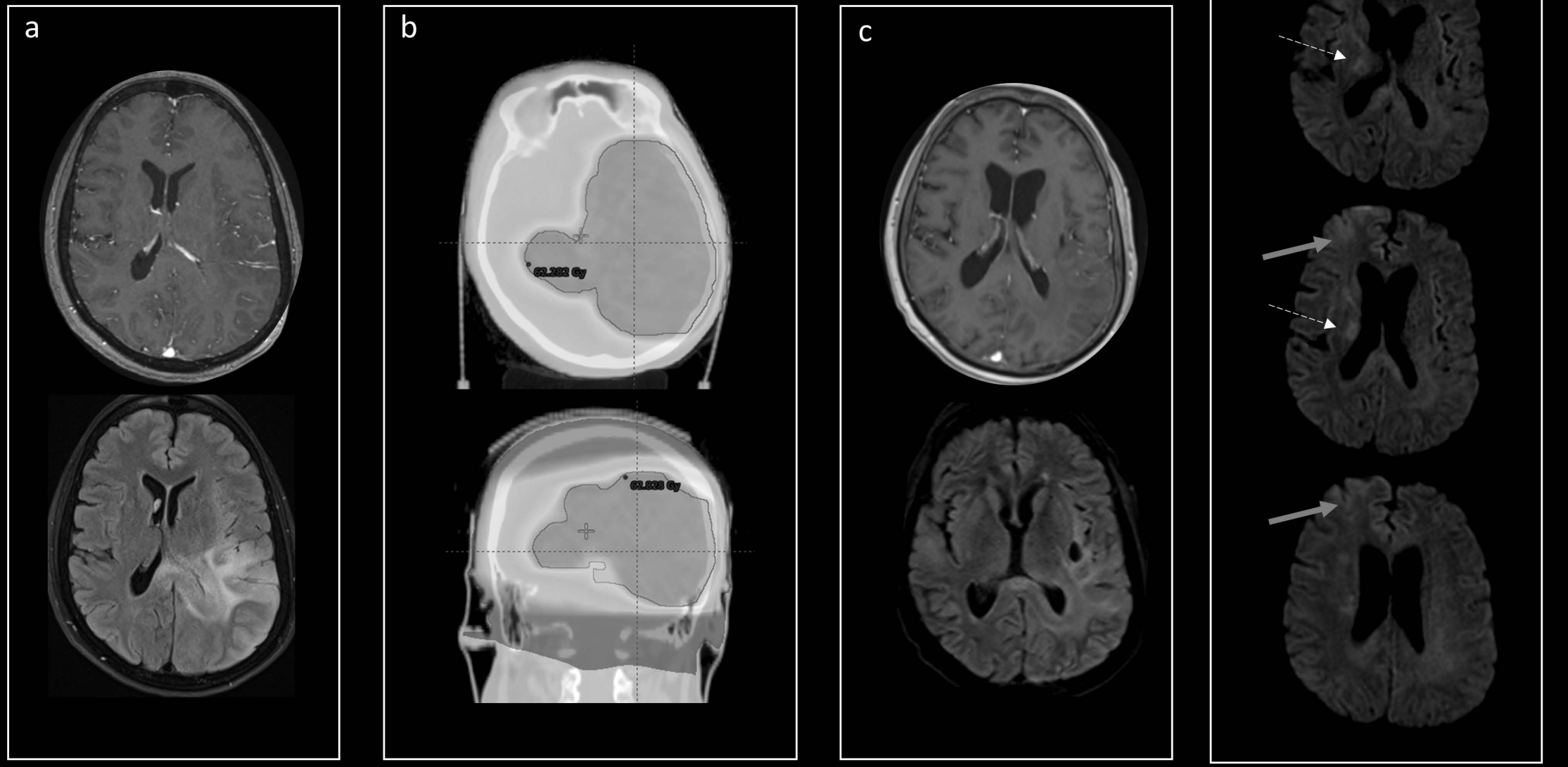
FIGURE LEGEND

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