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Case Report

Multiple sclerosis as differential diagnosis of radionecrosis for post-irradiation brain lesions: A case report

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ABSTRACT

Introduction: Demyelination can occur after brain radiotherapy in tissue adjacent to irradiated tumours. To date, no correlation has been found between conventional-dose radiotherapy and the development of multiple sclerosis, but radiotherapy could be a triggering factor among women with known multiple sclerosis. To the best of our knowledge, this is the first well-documented case of this association with a dosimetric analysis.

Case presentation: The case we report here describes the development of multiple sclerosis in a 36-year-old woman without significant past medical history 3 months after the last session of fractionated stereotactic radiotherapy for a pituitary macroadenoma. Our dosimetric analysis suggests that all the multiple sclerosis lesions occurred in the brain regions irradiated with a mean biologically effective dose (BED_2) of 33.9 Gy (27.3–49.6 Gy).

Conclusion: Consequently special caution towards radiotherapy is required among patients with demyelinating illnesses or for 35–45-year-old women who are at risk. In addition, multiple sclerosis lesions can look like metastases. We should therefore keep differential diagnoses in mind in order not to make mistakes that would delay treatment.

1. Introduction

Multiple sclerosis is a chronic immune-mediated demyelinating disease leading to neurological disorders, which needs to be diagnosed and treated early [1]. The revised 2017 Mc Donald criteria provide for a diagnosis of multiple sclerosis if cerebrospinal fluid (CSF)-specific oligoclonal bands are associated with a typical clinically isolated syndrome and clinical or MRI demonstration of dissemination. Symptomatic lesions can be used to prove dissemination in space or over time among patients with supratentorial, infratentorial or spinal cord syndrome [2].

Regarding brain radiation therapy, demyelination can occur in irradiated healthy brain parenchyma adjacent to the tumour [3]. Demyelination is one of the brain lesion know to be responsible for neurological toxicity [4,5]. This was first described in preclinical models of rats. Rats brain demyelination was both dose- and time-dependent, since it was only seen after 6 months and single doses of 17.5–25 Gy of X rays [6]. Then a post-mortem study of 25 patients treated with radiotherapy for glioma reported selective demyelination in tissues adjacent to the tumour [3].

To date, no correlation between conventional radiotherapy and the development of multiple sclerosis has been described or proved. It is generally only a triggering factor of multiple sclerosis flares among women with diagnosed disease [7]. This case report was prepared following the CARE Guidelines [8]. To our knowledge, this is the first case of multiple sclerosis after radiotherapy involving a woman without any past medical history and with an available dosimetric analysis to study correlations between multiple sclerosis lesions and the dose level of radiotherapy.

2. Case presentation

We report the case of a 36-year-old woman treated for a pituitary macroadenoma invading the left cavernous sinus revealed by headaches and decrease in visual acuity in the right eye. This

Abbreviations: BED, biologically effective dose; Gy, gray; CSF, cerebrospinal fluid; MRI, magnetic resonance imagery; CT, computed tomography; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; VMAT, volumetric modulated arctherapy; IMRT, intensity modulated radiotherapy; LS, Lhermitte's syndrome.

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macroadenoma was partially surgically resected in December 2015, which provided an improvement in her visual acuity but led to central diabetes insipidus and adrenal insufficiency. The pathological examination retained the diagnosis of FSH+ gonadotroph pituitary adenoma with a 4% cell proliferation of antigen KI-67.

In March 2018 magnetic resonance imagery (MRI) showed progression in the anterior and lateral parts of the left cavernous sinus, without visual symptoms. A further surgical resection was not feasible, and radiotherapy was decided in a dedicated multidisciplinary tumour board. The patient was treated with LINAC-based fractionated stereotactic radiotherapy using a NovalisTx® equipped with a high definition MultiLeaf Collimator (HD MLC 120) (Varian Medical Systems, Palo Alto, CA, USA). The treatment was performed with a non-invasive personalized thermoplastic mask, daily Exactrac® X-ray 6D system treatment positioning (Brainlab, Feldkirchen, Germany) and a robotic couch with 6° of leeway. Treatments were permitted when the setup error was under 0.7 mm translation and 0.7° rotation. The Gross Tumor Volume (GTV) was identified on the basis of 0.9 mm gadolinium-enhanced axial MRI fused with high-resolution computed tomography (CT) (1.25 mm slice thickness) (Fig. 1). The Clinical Target Volume (CTV) included the GTV, the bilateral cavernous sinus and the sella turcica. The CTV was then extended symmetrically by 2 mm in all dimensions to create the Planning Target Volume (PTV). The prescribed dose to the PTV was 50.4 Gy in 28 fractions of 1.8 Gy with Rapidarc® volumetric modulated arctherapy (VMAT). The VMAT plan was created with 2 coplanars arcs of 6 MV photons. Radiotherapy was performed from 11/05/2018 to 22/06/2018. No severe acute side effect was reported in the course of radiotherapy.

On August 10th 2018, i.e. 7 weeks after radiotherapy completion, the patient presented headaches with mandibular irradiation, which were related to trigeminal V3 neuralgia. No imaging was performed at this time. Treatment with 20 mg of oral prednisone daily for 5 days was introduced and was rapidly efficient. On September 2nd 2018, i.e. 10 weeks after radiotherapy completion, the patient reported a spontaneously resolving episode of decreased visual acuity. On September 24th 2018, i.e. 3 months after radiotherapy completion, the patient experienced a sudden worsening of symptoms with increased asthenia and hypoesthesia of the left hemi-arm associated with dizziness. A contrast-enhanced CT-scan was performed and showed stability of the pituitary adenoma without further anomalies. On the

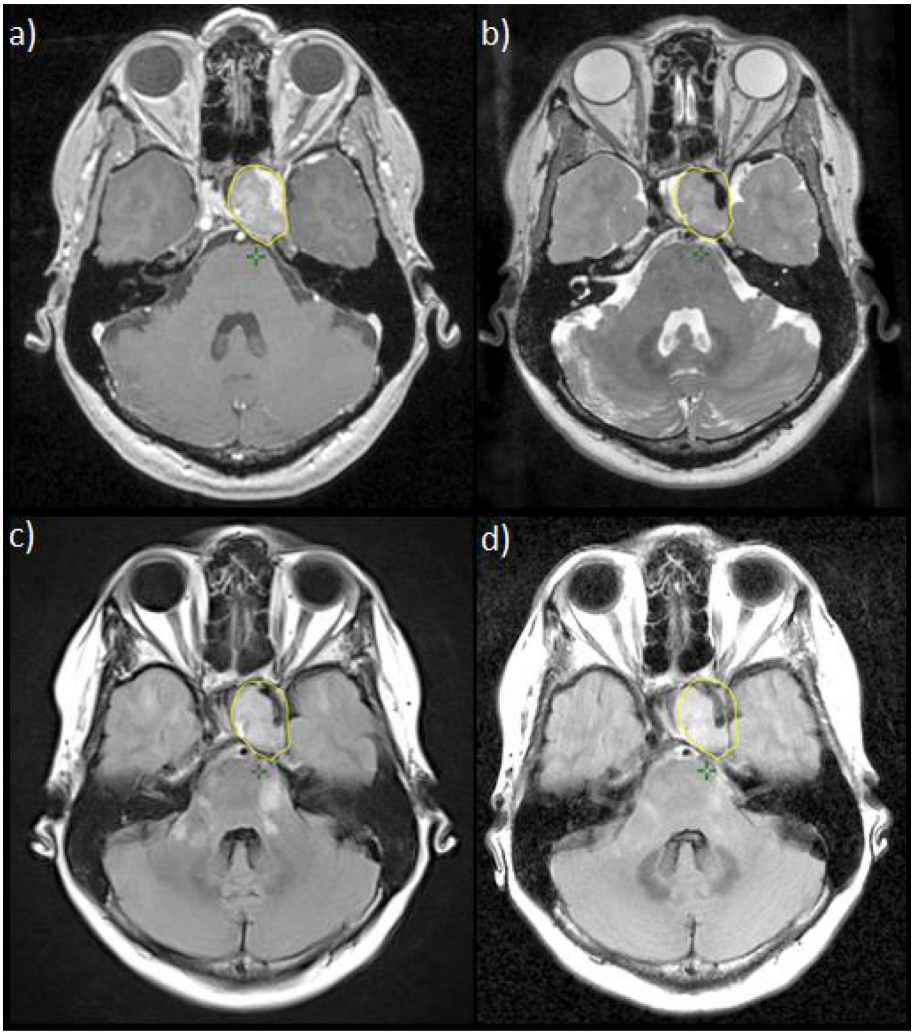

Fig. 1. Delineation of the pituitary macroadenoma on a 3D T1 Gadolinium-enhanced (a) and T2 (b) axial brain MRI performed in March 2018. Stability of the pituitary adenoma but appearance of multiple infra and supratentoriel T2 Flair hyperintense lesions, particularly in the posterior part of the brainstem and cerebellar peduncle and right Sylvian fissure, associated with discreet contrast-enhancing, on a T2 Flair axial Brain MRI performed in September 2018, i.e. 3 months after radiotherapy (c). Decrease in T2 hyperintense lesions on T2 Flair axial Brain MRI performed in November 2018 (i.e. 5 months after radiotherapy) after treatment with intravenous corticosteroids 1 g/day for 4 days (d).

same day, the patient was hospitalized in the Neurology Department. The neurological examination evidenced staggering gait with unipodal balance disorders, without kinetic cerebellar syndrome, horizontal multidirectional vertical nystagmus without oculomotor palsy, and hypoesthesia localized in V2 area with hypoacusis. No pyramidal syndrome or vesicosphincteric disorder was evidenced.

Brain MRI was performed on September 27th, 2018, i.e. 3 months after radiotherapy, and it evidenced stability of the pituitary adenoma but the appearance of multiple infra and supratentoriel T2 Flair hyperintense lesions, particularly in the posterior part of the brainstem and the cerebellar peduncle and the right Sylvian fissure, associated with discreet contrast-enhancing (Fig. 1). The patient underwent a lumbar puncture which evidenced a polyclonal intrathecal synthesis of immunoglobulin G (IgG), a cerebrospinal fluid protein concentration of 0.18 mg/mL and 7 white and 0 red corpuscles. All other tests were negative: negative antibody status for Lyme's disease, Varicella-Zoster Virus (VZV), Herpes Simplex Virus (HSV), Human Immunodeficiency Virus (HIV), Cytomegalovirus (CMV), Epstein Barr Virus (EBV), hepatitis B and C, and antiphospholipid antibody, and negative for RNA enterovirus detection, and for antinuclear antibodies, angiotensin-converting enzyme, Myelin Oligodendrocyte Glyprotein (MOG) Antibody and Aquaporin-4 protein. There was a slight folate deficiency at 0.48 ng/ml and negative cell co-culture. A thoraco-abdominopelvic CT-scan and a medullary MRI were performed and found no further lesions. It was concluded, using the 2017 McDonald criteria, that the clusters of clinical and paraclinical evidence indicated relapsing-remitting multiple sclerosis, PH-like (first clinical flare) and demyelinating central nervous system inflammatory disease with temporal and spatial dissemination (gadolinium-enhancing supra- and infratentorial lesions, cerebrospinal fluid-specific oligoclonal bands). A regional white matter Expert Panel confirmed this diagnosis in early November 2018.

Treatment of this primary progressive flare with intravenous corticosteroids (methylprednisolone) 1 g/day for 4 days was initiated and was effective, with improvement of all symptoms and a decrease in T2 hyperintense lesions on imaging (Fig. 1). On December 19th, 2018, i.e. 6 months after radiotherapy completion, the patient had severe asthenia and further neurological deterioration. A renewed treatment with corticosteroids 1 g/day for 3 days was carried out with improvement of all symptoms. Sustained treatment has been proposed because of the persistence of inflammatory lesions on MRI and V2 trigeminal dysesthesas. The patient first refused and later agreed after 3 weeks because of a re-emergence of weakness, nystagmus and new infratentorial lesions. Sustained treatment consisted in beta 1A Interferon (Avonex®). The patient was also offered a global rehabilitation program.

3. Discussion and conclusions

To our knowledge, only 4 cases of patients presenting multiple sclerosis following radiotherapy have been reported to date in the literature [7,9,10]. For these cases, no dosimetric analysis was performed. Shaygannejad et al. described the case of a 43-year-old woman without significant past medical history, treated for a meningioma with fractionated radiotherapy (28 sessions, no reported dose). She developed multiple sclerosis 9 months after radiotherapy [9]. Kemp et al described the case of a 65-year-old woman who developed multiple sclerosis 3.5 months after stereotactic radiosurgery for trigeminal neuralgia (90 Gy in 1 session). Doubt about a pre-existing treatment of trigeminal multiple sclerosis lesions was mentioned [10]. Milic et al. reported two cases: 39-year-old and 44-year-old women treated with radiotherapy (56 Gy in 30 sessions for the first and no reported dose for the second) for oligodendroglioma. They developed multiple sclerosis respectively 4 and 2 months after radiotherapy. The first patient had a lesion of the white matter before radiotherapy and the second had a history of transverse myelitis [7].

In summary, these 4 cases are all middle-aged women who developed multiple sclerosis after a mean time lapse of 4 months following radiotherapy. No data is available on the relationship between dose and multiple sclerosis occurrence. Most of these subjects already had a past medical history suggesting multiple sclerosis. External beam radiotherapy of the brain among patients with multiple sclerosis seems to be associated with an increase in neurotoxicity compared to patients without demyelinating disease [11].

We report here the case of a 36-year-old woman without significant past medical history who developed multiple sclerosis 3 months after the last session of fractionated stereotactic radiotherapy for a pituitary macroadenoma. This is in agreement with the few existing previous reports. The strength of our study is that it is the first to perform a dosimetric analysis to evaluate the correlation between the appearance of multiple sclerosis lesions and the doses received (Fig. 2). We identified 5 non-pre-existing areas of T2 Flair hyperintense lesions (Table 1). They received a mean dose of 23.1 Gy (20.1–31.7 Gy), a maximum dose (D2%) of 42.1 Gy (24.7–45.4 Gy) and a minimum dose (D98%) of 12.8 Gy (12.5–21.7 Gy). These results suggest that all multiple sclerosis lesions occurred in brain regions irradiated with a mean biologically effective dose (BED_2) of 33.9 Gy (27.3–49.6 Gy).

Demyelination is a known neurological side effect of radiation therapy. Even if a regional white matter Expert Panel confirmed the diagnosis of multiple sclerosis using the revised 2017 Mc Donald criteria and a sustained treatment with beta 1A Interferon (Avonex®) was effective, the diagnosis of multiple sclerosis remains uncertain and lesions described in this article may be also linked to another demyelination disease. That would not change treatment with corticosteroids and the correlation between demyelination and intermediate dose radiotherapy. As a comparison, spinal cord demyelination in form of Lhermitte's syndrome (LS) has been recently reported after chemo-intensity-modulated radiotherapy (chemo-IMRT) of head and neck cancer as one of the late term effects. LS is an electric shock-like sensation exacerbated by neck flexion that radiates down the spine and into extremities. It was first described in multiple sclerosis. It is caused by reversible demyelination of ascending sensory neurons due to inhibition of oligodendrocyte proliferation following radiotherapy of the cervical or thoracic spine. Pak et al. have observed a higher rate of LS after chemo-IMRT of head and neck cancer than the published rates after conventional radiotherapy [12]. Potential mechanisms of LS after IMRT are found in literature: greater mean dose, younger age and cord volumes receiving $\geq$30 and $\geq$40 Gy [12,13]. This is very interesting because demyelination seems to be correlate to intermediate dose radiotherapy, as observed in our case report.

To conclude, radiotherapy alone seems not to lead to multiple sclerosis lesions. However, radiotherapy could foster flares of multiple sclerosis. Special caution should therefore be exercised among patients with demyelinating disease undergoing radiotherapy, or women at risk between the ages of 35 and 45. In addition, multiple sclerosis lesions can look like metastases. This means we should keep the differential diagnoses in mind (metastasis, radionecrosis, ...) in order to avoid mistakes or delays in treatment. Demyelination after radiotherapy seems to associated with intermediate dose radiotherapy since it appears particularly in the irradiated brain with a mean BED_2 of 33.9 Gy (27.3–49.6 Gy).

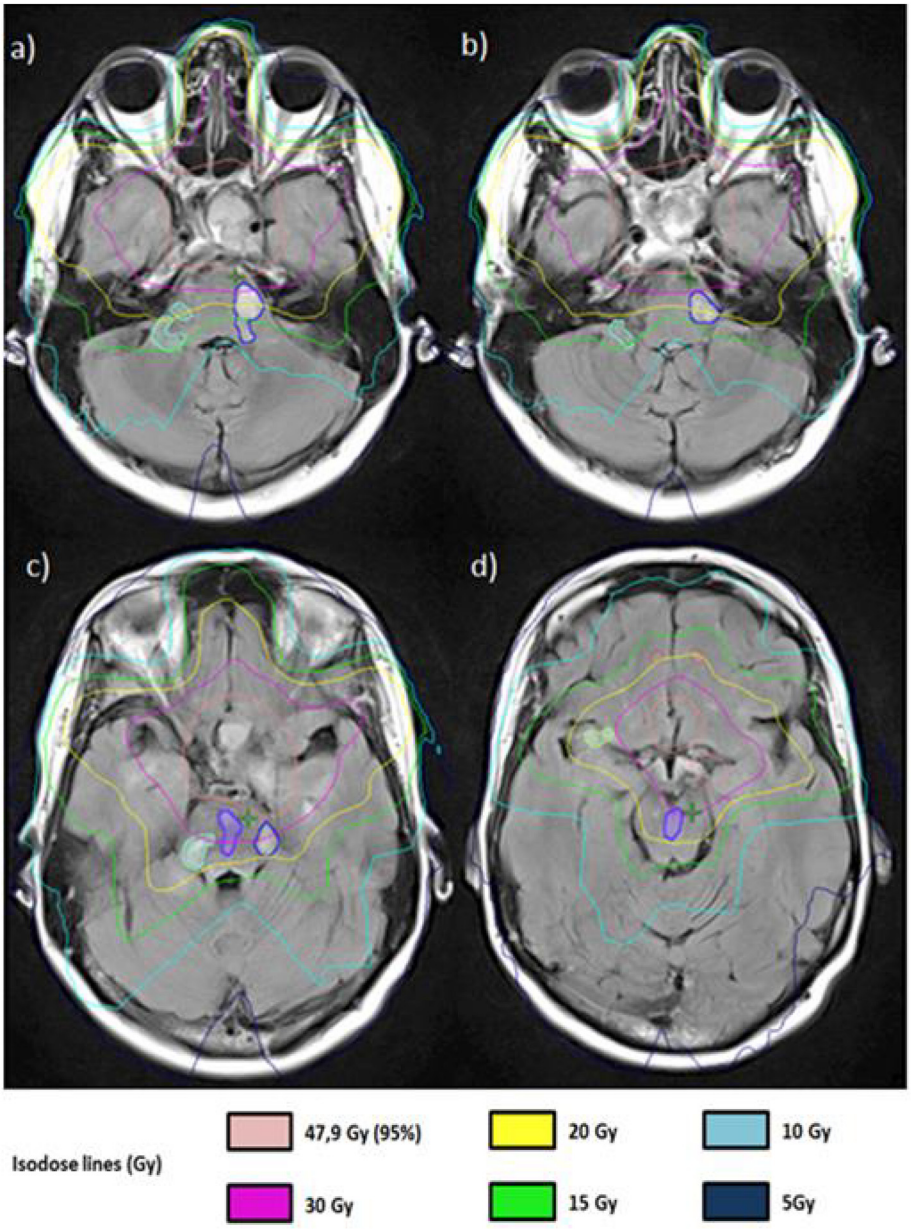

Fig. 2. Dosimetric analysis to evaluate the correlation between the appearance of multiple sclerosis lesions and the doses received. Five non-pre-existing areas of T2 Flair hyperintense lesions have been identified and delineated, as shown in the 4 different T2 FLAIR brain MRI axial planes, particularly in the posterior part of the brainstem and the cerebellar peduncle (a–c) and the right Sylvian fissure (d).

Table 1
Characteristics of the 5 non-pre-existing areas of T2 Flair hyperintense lesions occurring 3 months after radiotherapy.

Lesion	Localization	Dmean (Gy)	D98% (Gy)	D2% (Gy)	Mean BED_2 (Gy)
1	Brainstem + Right cerebellar hemisphere	23.6	12.5	45.4	33.5
2	Brainstem	31.7	21.7	43.1	49.6
3	Brainstem + Left cerebellar hemisphere	21.0	15.3	29.4	28.9
4	Inferior frontal gyrus	20.1	12.8	28.1	27.3
5	Right sylvian fissure	21.6	18.6	24.7	29.9
Total		23.1	12.8	42.1	33.9

Dx% (Gy) = dose (Gy) received by x% of the planning target volume. BED_2 = biologically effective dose calculated as $BED = D * (1 + d/(\alpha/\beta))$ with D = total dose, d = dose/session and $\alpha/\beta = 2$.

4. Ethics approval and consent to participate

Not applicable.

5. Consent for publication

A written informed consent to publish the report and associated medical images was obtained from the patient.

6. Availability of data and materials

All data generated or analysed during this study are included in this published article. If more data are needed, they are available from the corresponding author on reasonable request.

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8. Authors' contributions

FG and GD analysed the data, wrote and revised the manuscript. JB, SK and PC also revised the manuscript. All authors of this manuscript have actively participated in the data acquisition, and they all commented and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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