DR. GIULIA BERZERO (Orcid ID : 0000-0001-8798-9058)

DR. LUCA DIAMANTI (Orcid ID : 0000-0002-4540-6886)

Article type : Original Article

"Stroke-like" events after brain radiotherapy: a large series with long-term follow-up

Anna Luisa Di Stefano[1,2] MD PhD*, Giulia Berzero[3,4] MD*, François Ducray[5] MD PhD, Marica Eoli[6] MD, Anna Pichiecchio[7] MD, Lisa Maria Farina[7] MD, Valeria Cuccarini[8] MD, Marta Claudia Brunelli[9] MD, Luca Diamanti[3,4] MD, Stéphanie Condette Auliac[10] MD, Andrea Salmaggi[6,11] MD, Antonio Silvani[6] MD, Bruno Giometto[12] MD, Andrea Pace[13] MD, Antonello Vidiri[14] MD, Frederic Bourdain[1] MD, Stefano Bastianello[7,15] MD PhD, Mauro Ceroni[3,15] MD, Enrico Marchioni[3] MD

[1] *Department of Neurology, Hôpital Foch, Suresnes, France*

[2] *AP-HP Pitié-Salpêtrière, Service de Neurologie 2-Mazarin; Inserm U 1127, CNRS UMR 7225, Institut du Cerveau et de la Moelle épinière (ICM), Paris, France*

[3] *Neuroncology Unit, IRCCS Mondino Foundation, Pavia, Italy*

[4] *University of Pavia, PhD program in Biomedical Sciences, Pavia, Italy*

[5] *Department of Neuroncology, Hospices Civils de Lyon; Department of Cancer Cell Plasticity, Cancer Research Centre of Lyon, INSERM U1052, CNRS UMR5286, Lyon; Université Claude Bernard Lyon 1, F-69372, Lyon, France*

[6] *Neuroncology Unit, Fondazione Istituto Neurologico C. Besta IRCCS, Milan, Italy*

[7] *Neuroradiology Unit, IRCCS Mondino Foundation, Pavia, Italy*

[8] *Neuroradiology Unit, Fondazione Istituto Neurologico C. Besta IRCCS, Milan, Italy*

[9] *Department of Neurology, Ospedale Ca' Foncello, Treviso, Italy*

[10] *Department of Neuroradiology, Hôpital Foch, Suresnes, France*

[11] *SC Neurologia, Ospedale A. Manzoni, Lecco, Italy*

[12] *Department of Neurology, S. Antonio Hospital, Padova, Italy*

[13] *Neuroncology Unit, Regina Elena National Cancer Institute, Rome, Italy*

[14] *Radiology Unit, Regina Elena National Cancer Institute, Rome, Italy*

[15] *Department of Brain and Behavioral Sciences, University of Pavia, Italy*

* These authors contributed equally to the manuscript.

Corresponding Author:

Giulia Berzero, MD

Neuroncology Unit, IRCCS Mondino Foundation, Via Mondino 2, Pavia, Italy

Tel: + 39 382 380225; e-mail: giulia.berzero@mondino.it

Running title: “Stroke-like” events after brain radiotherapy

Keywords: brain tumor / radiotherapy / neurotoxicity / focal deficit / stroke / SMART syndrome / peri-ictal pseudoprogression (PIPG) / ALERT syndrome

Study Funding: The study had no targeted funding.

Disclosures: The authors have no conflicts of interest to disclose.

Acknowledgements: Anna Luisa Di Stefano was supported by "Premio Riquier".

Abstract

Background: Patients with history of brain radiotherapy can experience acute "stroke-like" syndromes related to the delayed effects of brain radiation, including "Stroke-like Migraine Attacks after Radiation Therapy (SMART)", "Peri-Ictal Pseudoprogression (PIPG)", and "Acute Late-onset Encephalopathy after Radiation Therapy (ALERT)" syndrome. The aim of this study is to collect evidence on the long-term outcome and treatment of these conditions, whose knowledge is undermined by their rarity and fragmented description.

Methods: Cases were collected, both prospectively and retrospectively, among six neuro-oncology departments. Inclusion criteria were: 1) history of brain radiotherapy (completed from at least 6 months); 2) new onset of acute/subacute neurological symptoms; 3) exclusion of all etiologies unrelated to brain irradiation. A review of current literature on "stroke-like" syndromes was performed to corroborate our findings.

Results: Thirty-two patients with acute neurological conditions attributed to the delayed effects of radiation were identified, including 26 patients with "stroke-like" syndromes. Patients with "stroke-like" syndromes commonly presented with a mosaic of symptoms, including focal deficits (77%), encephalopathy (50%), seizures (35%) and headache (35%). Seventy-three percent of them had acute consistent MRI alterations. Treatment included high-dose steroids in 65% of cases. Twenty-two patients recovered completely (85%). Sixteen

patients (62%) experienced relapses (median follow-up: 3.5 years). Literature review identified 87 additional "stroke-like" cases with similar characteristics.

Conclusions: "Stroke-like" events related to brain irradiation may be associated with permanent sequelae. Steroids are often administered on empirical grounds, as they are thought to accelerate recovery. Relapses are common, highlighting the need to elaborate adequate prevention strategies.

Introduction

Long-term survivors after brain radiotherapy can experience acute "stroke-like" events related to the delayed effects of brain irradiation. The description of these disorders is currently divided into three distinct entities: the "Stroke-like Migraine Attacks after Radiation Therapy (SMART)" syndrome [1-2], the "Peri-Ictal PseudoproGression (PIPG)" [3], and the "Acute Late-onset Encephalopathy after Radiation Therapy (ALERT)" syndrome [4]. Despite being described separately, these syndromes actually share a number of common features, including the long interval from brain irradiation, the acute onset, the association with transient enhancing MRI abnormalities, reversibility and recurrence. All these elements suggest that SMART, PIPG and ALERT may be different entities within the same spectrum of disorders. Although "stroke-like" syndromes have been described for over a decade, the rarity of these conditions, together with their delayed occurrence, hampers the realization of prospective studies, and current evidence is limited to isolated case reports or small case series. As a result, the knowledge on these syndromes remains fragmented and dispersed. To complicate this scenario, patients with history of brain radiotherapy may also experience actual strokes [5,6], and the potential relationship between stroke and "stroke-like" events related to brain irradiation is still unclear.

In the present study, we report a large series of patients with "stroke-like" events and an extensive review of the literature on this subject, with the aim of collecting evidence on the long-term outcome and treatment of these conditions.

Patients and methods

Present series

A multicentric study group on this topic, including six Institutions in Italy and France, was created in 2012. Patients were observed prospectively after the creation of the study group (2012-2017) or identified by retrospective review of institutional databases (1995-2011), using combinations of the following keywords: "brain tumor", "radiotherapy", "encephalopathy", "coma", "seizures", "headache", "focal deficit", "transient ischemic attack", and "stroke". Inclusion criteria were: 1) history of brain radiotherapy completed at least 6 months before the acute episode; 2) new-onset of acute/subacute neurological symptoms; 3) exclusion of all etiologies unrelated to the effects of radiation. Minimal diagnostic work-up included routine blood tests, brain MRI with contrast injection, and EEG. In patients with encephalopathy, CSF analysis with culture and search for herpesviruses was also required. Additional biological and instrumental assessments were taken into account case by case. After collective revision, only well-documented cases for which all alternative etiologies could be safely excluded were retained in the study. Two neuroradiologists (A.P., L.F.), independent from those who initially evaluated patient cases, reviewed MRI scans and identified recurrent imaging patterns. The study was approved by Institutional Ethics Committees.

Literature review

In order to substantiate our findings, we performed a review of the literature on ”stroke-like” syndromes. We performed a keyword search of Medline complemented by cross-checking citations. The keyword search of Medline was restricted to papers in English and French published between January 1995 and February 2018, and was performed using combinations of following keywords: “radiotherapy,” “neurotoxicity”, “headache”, “stroke-like”, “SMART syndrome”, “status epilepticus”, “peri-ictal pseudoprogression”, “coma”, and “ALERT syndrome”. Supplementary Figure 1 reports the algorithm for paper selection.

Results

Present series

Thirty-two patients were identified (15 prospective and 17 retrospective cases), including seven cases that had been previously published (patients n°1-5 in [4] and patients n°10-11 in [3]). All 32 patients had acute neurological conditions attributed to the delayed effects of radiation: 6 patients had small vessel infarcts and 26 patients had “stroke-like” events.

”Stroke-like” events

Table 1 reports previous tumor history, clinical-paraclinical features at the time of the acute episode, treatment and outcome in the 26 patients with “stroke-like” events (patients n°1-26).

Previous tumor history

All patients had received brain irradiation. The indications to brain radiotherapy included primary brain tumors (62%), systemic malignancies (27%), intracranial extradural tumors (8%), and vascular malformations (4%). The median age at the time of radiotherapy was 37 years-old (range 4-69). Twelve patients had received focal radiotherapy (46%) and 13

patients whole brain (WBRT) or craniospinal radiotherapy (50%); the remaining patient (patient n°8) had received both radiotherapy types. Fifteen patients had received systemic chemotherapy (58%). Three patients had a history of intrathecal chemotherapy (12%).

Clinical and paraclinical features at the time of the acute episode

The acute episode occurred after a median delay of 10 years from brain radiotherapy (range 0.75-43). Acute neurological symptoms were preceded (or accompanied) by fever in 7 cases (27%) and by elevated blood pressure in one (4%). Clinical presentation was generally characterized by a mosaic of symptoms, including focal deficits (77%), encephalopathy (50%), headache (35%) and seizures (35%). Brain MRI ruled out tumor recurrence and showed mild to severe chronic post-actinic changes in all patients (including progressive leukoencephalopathy, microbleeds, and cortical atrophy). Over this chronic ground, 19 out of the 26 patients (73%) had the appearance of acute enhancing MRI alterations. Acute MRI abnormalities were in all cases consistent with acute neurological symptoms and located within brain areas that received irradiation. Based on clinical and MRI features at the time of the acute episode, three clinical-radiological groups were identified:

- ALERT syndrome (patients n°1-7): Patients in this group had encephalopathy and/or seizures, associated with "stroke-like" deficits and/or headache. Encephalopathy ranged from mild psychomotor slowing to severe vigilance impairment, and was the dominant clinical feature in most patients. In four out of the seven patients (57%), MRI showed acute multifocal abnormalities in the subcortical and/or periventricular white matter characterized by punctuate or ring contrast enhancement (Figure 1). The remaining 3 patients had normal MRI findings. All seven patients had received WBRT, explaining the diffuse/multifocal involvement observed on clinical and radiological grounds.

- SMART syndrome and PIPG (patients n°8-22): Patients in this group had focal "stroke-like" deficits and/or mild encephalopathy, associated with headache and/or seizures. In all 15 patients, MRI showed a unilateral cortical-subcortical area of hyperintensity and swelling on T2/FLAIR images, with prominent cortical enhancement on T1-gad (Figure 2). The pattern of contrast enhancement was multilobar and gyriform, as reported in classical SMART cases [2,3], or nodular and peritumoral, as reported in PIPG [4]. The clinical and MRI features of patients in this group corresponded to a strictly unilateral hemispheric dysfunction and, consistently, 12 out of the 15 patients (80%) had received focal radiotherapy over the affected hemisphere.

- Short-lasting focal deficits (patients n°23-26): Patients in this group had recurrent episodes characterized by short-lasting (1-12 hours) focal deficits without headache or other accompanying symptoms. None of them had acute abnormalities on MRI. All four patients underwent a thorough cerebrovascular assessment (carotid ultrasound, intracranial angio-CT or MR-angiogram, thrombophilic panel, ECG, and transthoracic echocardiogram) but no arguments for an atherothromboembolic etiology were found. Clinical characteristics and repeated EEG testing ruled out an epileptic mechanism. Three patients out of the four had received whole-brain or craniospinal radiotherapy (75%); two of them had also received intrathecal chemotherapy (50%).

Treatment and outcome

Seventeen out of the 26 patients with "stroke-like" events were treated with high-dose steroids on empirical grounds (65%). Twenty-two patients recovered completely (85%), with a median time to recovery of 14 days (range 1-90). Four patients were left with permanent sequelae (15%). Three patients among the latter ultimately developed a steroid-dependent course (i.e., worsening of neurological symptoms at steroid tapering) and died because of steroid-related complications. Acute enhancing MRI alterations (whenever present) resolved

in 3 to 8 months in all cases. Sixteen patients experienced relapses of "stroke-like" events during follow-up (62%), involving the same and/or the contralateral hemisphere (if the latter had received irradiation). Median follow-up duration was 3.5 years (range 0.5-20).

Small vessel infarcts

Table 2 reports previous tumor history, clinical-paraclinical features, treatment and outcome in the six patients experiencing small vessel infarcts (patients n°27-32). Five patients had received focal radiotherapy and one patient whole-brain radiotherapy. The median age at the time of radiotherapy was 34.5 years old (range 17-70). Stroke occurred after a median delay of 12 years after brain irradiation (range 1-32). The ischemic area was located in the periventricular white matter in four cases and in the thalamocapsular region in two (Figure 3). In all cases, the ischemic lesion was congruous with acute neurological symptoms and located within the radiation port. No source of cardiac or carotid thromboembolism was found. Intracranial vessel evaluation (by MR-angiography, CT-angiography, or ultrasound) disclosed multiple non-critical stenoses in the vessels included in the radiation port. Five patients out of the six were given antiplatelets. Five patients recovered completely (83%) in 7 to 15 days. Four patients had subsequent small vessel infarcts (67%) in the same or in other vascular territory involved by radiation.

Literature review

Literature review identified 87 cases of "stroke-like" syndromes after brain irradiation (Supplementary Table 1). The indications to brain radiotherapy included primary brain tumors (71%), systemic malignancies (26%) and intracranial extradural tumors (2%). The median age at the time of radiotherapy was 31 years-old (range 5-71). The acute episode occurred after a median delay of 13 years (range 1-35) from brain radiotherapy. Clinical

presentation included "stroke-like" deficits (87%), headache (72%), seizures (63%), and encephalopathy (41%). Eighty-six percent of patients had acute consistent MRI alterations. Twenty-eight percent of patients received high-dose steroids. Seventy-nine percent of patients recovered completely. Follow-up information is reported in only 40% of cases. Fifty-six percent of patients experienced relapses of "stroke-like" events during follow-up (median duration: 1.5 years; range 0.25-14).

Discussion

This study reports a large original series of patients with "stroke-like" events related to the delayed effects of brain irradiation (n=26) together with a comprehensive review of the literature on this subject (n=87). The strong point of the study is the magnitude of the resulting cohort (n=113), which allows to draw solid considerations on the clinical-radiological profile and the long-term outcome associated with these conditions. The main limitations of the study concern the lack of details on the total dose and fractionation of radiotherapy, as radiation was administered decades before the acute episode or was performed in other centers, and the fact that steroid administration was not carried out according to standardized protocols, limiting our capacity to conclude on its efficacy.

Table 3 summarizes the clinical-radiological features of "stroke-like" syndromes in our series and in literature. Despite the different indications, all patients had received brain radiotherapy. The indication to brain irradiation was represented by CNS localizations of systemic malignancies in one quarter of cases (27% of patients in our series vs. 26% in literature). Radiotherapy was whole-brain or craniospinal in half of cases (52% of patients in our series vs. 47% in literature), which is remarkable considering the rarity of this treatment modality. The "stroke-like" episode occurred a decade after brain irradiation (median delay: 10 years in our series vs. 13 years in literature), although delays as short as 9 months were

also observed. Neurologists should keep in mind that "stroke-like" events are not exclusive to patients with primary brain tumors or to long-term survivors.

Neurological presentation was characterized by a mosaic of symptoms, of variable severity and duration. "Stroke-like" deficits were present in the vast majority of patients (77% of patients in our series vs. 87% in literature). Whenever present (35% of patients in our series vs. 63% in literature), seizures had a focal onset and arose from the same hemisphere responsible for "stroke-like" deficits. Encephalopathy, ranging from mild psychomotor slowing to severe vigilance impairment, was a frequent accompanying feature (50% of patients in our series vs. 41% in literature).

Acute enhancing MRI alterations, located multifocally in the white matter (ALERT, Figure 1) or unilaterally in the cortical-subcortical region (SMART/PIPG, Figure 2), were detected in the majority of patients (73% of patients in our series vs. 86% in literature). The remaining proportion of patients, including some with severe vigilance impairment (patients n°2,3,5), had normal findings on MRI, highlighting that nor the presence, or the extent, of acute MRI alterations correlates with clinical severity. Despite being reported as separate entities, in the present series, we grouped SMART syndrome and PIPG in the same clinical-radiological category, based on the observation that they shared the same pattern of unilateral cortical dysfunction, in contrast to ALERT patients who displayed a bilateral multifocal impairment.

Steroids are thought to accelerate recovery and thus are often administered in these conditions on empirical grounds. Sixty-five percent of "stroke-like" patients in our series (vs. 28% in literature) received high-dose steroid treatment. Steroid efficacy was evident in ALERT patients, who experienced rapid vigilance restoration within few days from steroid introduction, while, in patients with SMART or PIPG, a neat temporal correlation between steroid introduction and clinical improvement could not be established. Brain irradiation has been associated with vasculitic changes within the wall of small and medium-sized vessels

[7], and this might account for the efficacy of steroid treatment observed in ALERT cases. Antiplatelets administered to three out of the four patients with short-lasting focal deficits in our series under the assumption of an atherothrombotic mechanism, but this therapy did not prevent them from experiencing subsequent similar episodes. Their clinical characteristics, together with the lack of alternative causes, suggest that these episodes might correspond to amputated episodes of SMART lacking of a radiological correlate.

Complete recovery was observed in the 85% of patients in our series (vs. 79% in literature), although in some cases it took weeks to months to fully occur. Permanent neurological deficits concerned a non-negligible proportion of patients (15 in our series vs. 21% in literature), confirming that "stroke-like" syndromes are not always reversible as initially thought [2, 4]. The occurrence of cortical infarcts is one, but not the sole, mechanism that can be responsible for permanent sequelae during SMART episodes (Supplementary Figure 2) [2]. Relapses were highly common (62% in our series vs. 56% in literature), highlighting the need to elaborate adequate prevention strategies.

Patients with history of brain irradiation seem prone not only to "stroke-like" events but also to actual strokes, and whether these two groups of conditions are related is still unclear. In our series, we did not observe major strokes due to large vessel thrombosis. This probably reflects a selection bias, as all recruiting centers were neuro-oncology departments and, therefore, did not admit patients with large vessel strokes. All stroke cases in our series corresponded to small vessel infarcts attributed to previous brain radiation. Patients experiencing small vessel infarcts shared some common features with patients experiencing "stroke-like" events, including previous treatment modalities, acute clinical presentation, and relapse rate. These similarities, together with the observation that some patients with "stroke-like" syndromes (patients n°20, 26) also had antecedents of small vessel strokes, suggest that these two groups of conditions might share a common pathological substrate. This substrate

could reside in the permanent endothelial dysfunction induced by radiation [8], leading alternatively to transient blood-brain barrier disruption (SMART syndrome) or to thrombosis and infarct (small vessel strokes). However, further evidence is needed to clarify the etiology of the syndromes and elaborate adequate prevention strategies.

References

1. Black DF, Bartleson JD, Bell ML, Lachance DH. SMART: stroke-like migraine attacks after radiation therapy. Cephalalgia. 2006 Sep;26(9):1137-1142.

2. Black DF, Morris JM, Lindell EP, et al. Stroke-like migraine attacks after radiation therapy (SMART) syndrome is not always completely reversible: a case series. American Journal of Neuroradiology 2013 Dec;34(12):2298-2303.

3. Rheims S, Ricard D, van den Bent M, et al. Peri-ictal pseudoprogression in patients with brain tumor. Neuro-oncology 2011 Jul;13(7):775-782.

4. Di Stefano AL, Berzero G, Vitali P, et al. Acute late-onset encephalopathy after radiotherapy: an unusual life-threatening complication. Neurology. 2013 Sep 10;81(11):1014-1017.

5. Kreisl TN, Toothaker T, Karimi S, DeAngelis LM. Ischemic stroke in patients with primary brain tumors. Neurology. 2008 Jun 10;70(24):2314-2320.

6. Plummer C, Henderson RD, O'Sullivan JD, Read SJ. Ischemic stroke and transient ischemic attack after head and neck radiotherapy: a review. Stroke. 2011 Sep;42(9):2410-2418.

7. Rauch PJ, Park HS, Knisely JP, Chiang VL, Vortmeyer AO. Delayed radiation-induced vasculitic leukoencephalopathy. Int J Radiat Oncol Biol Phys. 2012 May 1;83(1):369-375.

8. Hopewell JW, van der Kogel AJ. Pathophysiological mechanisms leading to the development of late radiation-induced damage to the central nervous system. Frontiers of Radiation Therapy and Oncology 1999;33:265-275.

Figure Legends

Figure 1. MRI findings in patients with ALERT syndrome. Patient n°4. Two focal hyperintensities in the left rolandic subcortical region in the context of multiple confluent white matter lesions on FLAIR images, with patchy enhancement on T1 gad. **Patient n°6:** multiple bilateral focal subcortical and periventricular hyperintensities on FLAIR images, with patchy enhancement on T1 gad. **Patient n°7:** multiple focal areas of hyperintensity in left periventricular white matter and corpus callosum on FLAIR images, some of which show mild contrast enhancement on T1 gad; focal hyperintensity with mild mass effect in the left anterior periventricular region with ring contrast enhancement.

Figure 2. MRI findings in patients with SMART syndrome and PIPG. Patient n°9: right cortical parietal hyperintensity on FLAIR images with focal diffusion restriction on DWI/ADC and gyriform enhancement on T1 gad. **Patient n°12:** right temporo-parieto-occipital cortico-subcortical hyperintensity and swelling on FLAIR images, with partial diffusion restriction on DWI/ADC, and marked cortical enhancement on T1gad. **Patient n°13:** right temporo-occipital cortical-subcortical hypersignal and swelling on FLAIR images, with diffusion restriction on DWI/ADC and cortical-subcortical enhancement on T1

gad. **Patient n°22:** right cortical peritumoral gyriform hyperintensity on DWI B1000, associated with partial ADC hyposignal and neat cortical enhancement on T1 gad.

Figure 3. MRI findings in patients with small vessel infarcts. Patient n°28: left capsulo-putaminal nodular hyperintensity on FLAIR and DWI B1000, without diffusion restriction on ADC (MRI performed 13 days after acute onset). **Patient n°29:** multiple foci of restricted diffusion on DWI /ADC in posterior deep white matter. Note multiple bilateral susceptibility foci on T2* , mainly in the right hemisphere. **Patient n°31:** focal area of hypersignal in left periventricular white matter on FLAIR and DWI B1000. Note T2* diffuse bilateral focal susceptibility foci in the bihemispheric white matter. **Patient n°32:** focal area of hypersignal in right thalamus on FLAIR images, with correspondent diffusion restriction in DWI/ADC.

Table 1. Previous tumor history, clinical and paraclinical features at the time of the acute episode, treatment and outcome in the 26 patients with "stroke-like" events (patients n°1-26).

			TUMOR HISTORY			CLINICAL AND PARACLINICAL FEATURES AT THE TIME OF THE ACUTE EPISODE		MRI CHARACTERISTICS				TREATMENT AND OUTCOME					
Pt	**Sex**	**Age at RT**	**Type, location, side**	**Treatment**	**Delay since RT (yrs)**	**Clinical presentation**	**EEG**	**T2/FLAIR**	**DWI b1000/ADC**	**T1 gad**	**Final diagnosis**	**Treatment**	**Recovery (residual deficit)**	**Time to recovery (days)**	**Relapse (side)**	**Final outcome**	**FU since 1st ep. (yrs)**
1	M	30	Gr. III Astro, F, L	Su; WBRT (60 Gy); Ch	6	Stupor (GCS 4), Aphasia, Right hemiplegia, Left arm decorticated posturing	Left depression	No cortical HS No cortical-subcortical abnormalities	n.a.	Multiple bilateral (mainly left) cortico-subcortical areas of patchy Enh	**ALERT**	IV MP 1 gr daily (5 days), oral steroids tapering, AED	Partial (hemiparesis)	14	Yes (ipsil. and contral.)	Death for pneumonia	2,5
2	M	37	Gr. II Oligo, F, L	WBRT (60 Gy); Ch	17	Confusion, Coma (GCS 3), Visual hallucinations, Dysphagia	Diffuse slowing with left prevalence	No cortical HS No cortical-subcortical abnormalities	No diffusion restriction	No Enh	**ALERT**	IV MP 1 gr daily (5 days), oral steroids tapering, AED	Complete	20	No	Tumor stable disease	6
3	M	17	Gr. III Meningioma, P, L	Su; WBRT (60 Gy)	10	Headache, Stupor (GCS 4),	Diffuse slowing (right	No cortical HS No cortical-	n.a.	No Enh	**ALERT**	IM DXM 16 mg daily, oral	Partial (paraparesis,	24	Yes (ipsil.)	Death for pneumo	2

					Alternating-side partial motor seizures	prevalence); isolated epileptic discharges	subcortical abnormalities				steroids tapering, AED	cognitive decline)			nia	
4	M	21	CNS involvement of NHL	WBRT (30 Gy)	0,75	Stupor (GCS 10), Headache, Aphasia, Right hemiparesis	Right T-O spike-slow waves complexes	Left rolandic subcortical focal hyperintensities	Left rolandic subcortical focal restriction	Bilateral (mainly left) rolandic subcortical patchy Enh	**ALERT**	IV MP 1 gr daily (5 days), oral steroids tapering, AED	Complete	12	Yes (contral.)	Tumor complete remission	6
5	F	58	Single metastasis, Cerebell	Su; WBRT (30 Gy)	6	Stupor (GCS 8), Headache, Aphasia, Right hemiplegia, Right facio-brachial dystonic seizures	Bifrontal slow abnormalities	No cortical HS No cortical-subcortical abnormalities	No diffusion restriction	No Enh	**ALERT**	IV MP 1 gr daily (5 days), oral steroids tapering, AED	Complete	4	No	Tumor stable disease	1,4
6	M	25	Choriocarcinoma, pineal	Su; WBRT; Ch	4	Psychomotor decline, Global Motor Impairment	No epileptic abnormalities	Multiple bilateral focal subcortical and periven. areas of HS	n.a.	Multiple bilateral subcortical and periven. areas of patchy Enh	**ALERT**	AED	Partial (worsening neuropsy. background)	45	No	Tumor remission	6

7	M	20	Brain metastasis, P, L	Su; WBRT; radiosurgery	2	Right partial motor seizures	No epileptic abnormalities	Multiple focal areas of HS in corpus callosum and left periven. WM	n.a.	Ring Enh of the left anterior periven. lesion	**ALERT**	Steroids, AED	Complete	3	Yes (ipsil.)	Systemic tumor progression 9 years after 1 st ep.	9
8	M	4	Medullo, Cerebell, L	Su; CSRT	43	Psychomotor decline, Global motor impairment	Bilateral diffuse slow abnormalities	Left P-O cortical HS and swelling	Left P-O foci of cortical HS on b1000 (ADC n.a.)	Left P-O cortical gyriform Enh	**SMART/ PIPG**	IV DXM 8 mg daily (15 days) followed by tapering, antivirals, antibiotics	Complete	15	No	Tumor stable disease	0,5
		45	Gr. III Meningioma, P-O, R	Su; RT	2												
9	M	53	Single metastasis, T, R	Su; WBRT (30 Gy), Ch	7	Psychomotor slowing, Left motor seizures	Right T-P-O epileptic discharges	Right T-P-I cortical-iuxtacortical HS and swelling	Right T-P focal diffusion restriction	Right T-P gyriform Enh	**SMART/ PIPG**	AED, Steroids	Complete	53	Yes (ipsil.)	Tumor remission	5
10	M	44	GBM, P-O, R	Su; RT; Ch	5	Drowsiness, Dysarthria, Left arm progressive sensory disturbance, Left partial	Right T-P epileptic discharges	Right T-P HS involving both cortex and subcortical-deep WM	n.a.	Right T-P cortico-subcortical Enh	**SMART/ PIPG**	Oral prednisone 40 mg daily (7 days) followed by	Complete	7	Yes (ipsil.)	Tumor complete response	11

					sensory seizures						tapering, AED					
11	M	42	Gr. III Oligo, F-T, R	Su; RT; Ch	3	Drowsiness, Left hemiparesis, Left partial motor seizures	Right F epileptic discharges	n.a.	n.a.	Right F-I-T lepto. and cortical-subcortical Enh	**SMART/ PIPG**	Oral prednisone 40 mg daily (7 days) followed by tapering, AED	Complete	21	Yes (ipsil.)	Tumor stable disease	5
12	M	16	Meningosarcoma, F-T, R	Su; RT (60 Gy)	32	Psychomotor slowing, Aphasia, Left hemiparesis, Left LHH	Right slow and epileptic abnormalities	Right T cortical-subcortical HS and swelling	Right T cortical diffusion restriction	Right T cortical Enh	**SMART/ PIPG**	IV MP 1 gr daily (5 days), oral steroids tapering, AED	Complete	90	No	Tumor remission	1,1
13	M	35	Grade II Astro, Cerebell, R	Su; RT	17	Confusion, Headache, Left LHH	Right F-T slow abnormalities	Right T-P-O cortical-subcortical HS and swelling	Right T-P-O diffusion restriction	Right T-P-O cortical-subcortical Enh	**SMART/ PIPG**	IV MP 1 gr daily (5 days), oral steroids tapering	Complete	8	No	Tumor stable disease	1,5
14	M	69	Gr. II Oligo, T-P, R	Su; RT; Ch	12	Confusion, Headache, Left arm motor deficit, Left LHH	Right F-T slow abnormalities	Right T-P mild cortical HS	Right T-P diffusion restriction	Right T-P cortical-subcortical Enh	**SMART/ PIPG**	IV MP 125 mg daily (5 days), oral steroids tapering,	Complete	14	Yes (ipsil.)	Tumor stable disease	3

											AED					
15	F	42	CNS involvement of NHL	WBRT (40Gy)	17	Headache, Aphasia, Right hemiplegia, Right partial motor seizures	Left hermispheric slow abnormalities	Left hemispheric cortical HS	Left hemispheric subcortical diffusion restriction	Left hemispheric cortical gyriform Enh	**SMART/ PIPG**	IV DXM 40 mg daily followed by tapering, antivirals, antibiotics, AED	Partial (hemiparesis, aphasia)	90	Yes (ipsil.)	Death for pneumonia	0,75
16	M	53	Gr. III Astro, T-P, L	Su; RT (60 Gy); Ch	10	Headache, Aphasia	Left T focal slow abormalities	Left T-P cortical-subcortical HS and swelling	n.a.	Left T-P punctuate cortical Enh	**SMART/ PIPG**	DXM 4 mg daily (3 months), antivirals	Complete	20	Yes (ipsil.)	Tumor stable disease	3
17	F	37	Gr. III Astro, P, L	Su; RT (60 Gy); Ch	20	Headache, Aphasia, Right hemiparesis	Infraclinical left F epileptic discharges	Left F-P cortical-subcortical HS	Left F cortical focal diffusion restriction	Left rolandic patchy cortical Enh	**SMART/ PIPG**	NSAID, AED	Complete	6	No	Tumor stable disease	3
18	M	28	Plasmocytoma, left nasal fossa	RT	20	Headache, Right LHH	Left T slow and epileptic abnormalities	Left O cortical-subcortical HS and mild swelling	Left O partial focal restriction	Left O cortical Enh	**SMART/ PIPG**	AED, Antiplatelets	Complete	18	No	Tumor remission	1
19	M	61	Chondrosarcoma,	Su; RT; Ch	5	Aphasia, Right LHH, Right	Left T slow	Left P-O cortical hyperdensity and swelling with cortical gyriform Enh			**SMART/**	AED	Complete	12	Yes (ipsil.	Tumor remissio	11

		P, L		focal seizures	post-ictal abnormalities	(head CT with contrast)			**PIPG**				)	n	
20	M	14	Medullo, Cerebell	Su; CS RT; intrathecal Mtx; Ch	28	Left partial sensory seizures, Left LHH	Left hemispheric slow abnormalities	Right T-P-O cortical HS and swelling	Right T-P-O cortical HS on b1000, partial ADC restriction	Right T-P-O cortical Enh	**SMART/ PIPG**	IV MP 1 gr daily (5 days), oral steroids tapering, AED, Antiplatelets	Complete	15	Yes (ipsil. and contral.)	Tumor stable disease	6
21	M	32	Cavernous angioma, Pons	RT	33	Right LHH	Left T focal slow abnormalities	Left O cortical HS	No diffusion restriction	Left O gyriform Enh	**SMART/ PIPG**	IM DXM 8 mg daily (8 days) followed by tapering	Complete	12	No	Tumor stable disease	9
22	M	48	Gr. II Oligo-Astro, O, R	Su; RT; Ch	8	Left arm paresis	Right T focal slow and epileptic abnormalities	n.a.	Right T-P cortical HS on b1000, partial ADC restriction	Right T-P peritumoral gyriform Enh	**SMART/ PIPG**	AED	Complete	21	No	Tumor stable disease	3
23	F	39	Gr. II Oligo, F, L	Su; Ch; RT (60Gy)	11	Dysarthria, Right-sided sensory disturbance, Right hemiparesis	Left focal slow waves	No cortical HS No cortical-subcortical abnormalities	No diffusion restriction	No Enh	**SHORT-LASTING FOCAL**	Antiplatelets, AED	Complete	< 12 hours	Yes (ipsil.)	Tumor stable disease	4

									DEFICITS						
24	F	26	Medullo, Cerebell, R	Su; CSRT; intrathecal Mtx+Ara-C; Ch	17	Aphasia	No abnormalities	No cortical HS No cortical-subcortical abnormalities	No diffusion restriction	No Enh	**SHORT-LASTING FOCAL DEFICITS**	Antiplatelets, AED	Complete	1 hour	Yes (ipsil.)	Tumor remission	1,75
25	M	55	Small cell lung cancer	Prophylactic WBRT (36 Gy); Ch	6	Aphasia, Left sensory deficit	Right T-P-O slow abnormalities	No cortical HS No cortical-subcortical abnormalities	No diffusion restriction	No Enh	**SHORT-LASTING FOCAL DEFICITS**	None	Complete	1,5 hours	Yes (ipsil.)	Tumor remission	5
26	M	23	CNS involvement of NHL	WBRT; intrathecal Mtx	12	Dysarthria	No abnormalities	No cortical HS No cortical-subcortical abnormalities	No diffusion restriction	No Enh	**SHORT-LASTING FOCAL DEFICITS**	Antiplatelets	Complete	< 4 hours	Yes (ipsil. and contral.)	Tumor remission	20

Legend to Table 1. Abbreviations: Ara-c: cytarabine; AED: antiepileptic drugs; Astro: astrocytoma; Cerebell: cerebellum; Ch: chemotherapy; contral.: contralateral; CS: craniospinal; DXM: dexamethasone; Enh: enhancement; F: frontal; GBM: glioblastoma; GCS: Glasgow Coma Scale; Gr: grade; HS: hypersignal; ipsil.: ipsilateral; I: insular; L: left; LHH: lateral homonymous hemianopia; Medullo: medulloblastoma; MP: methylprednisolone; Mtx: Methotrexate; n.a.: not available; neuropsy.: neuropsychiatric; NHL: non-Hodgkin lymphoma; NSAID: non-steroidal anti-inflammatory drugs; O: occipital; Oligo: oligodendroglioma; P: parietal; PCNSL: primary central nervous system lymphoma; periven.: periventricular; R: right; RT: radiotherapy; Su: surgery; T: temporal; WBRT: whole brain radiotherapy; WM: white matter.

Table 2. Previous tumor history, clinical and paraclinical features, treatment and outcome in the 6 patients with small vessel infarcts (patients n°27-32).

			TUMOR HISTORY			**CLINICAL AND PARACLINICAL FEATURES AT THE TIME OF THE ACUTE EPISODE**						**TREATMENT AND OUTCOME**				
								MRI CHARACTERISTICS								
Pt	**Sex**	**Age at RT**	**Type, location, side**	**Treatment**	**Delay since RT (yrs)**	**Clinical presentation**	**EEG**	**T2/FLAIR**	**DWI b1000/ADC**	**T1 gad**	**Final diagnosis**	**Treatment**	**Recovery (residual deficit)**	**Time to recovery (days)**	**Relapse (side)**	**Final outcome**	**FU since 1st ep. (yrs)**
27	M	31	PCNSL, Cerebell	Su; RT; Ch	12	Right sensory deficit	No abnormalities	Left deep insular periventricular focal HS	Left insular nodular hyperintensity on b1000 without	Left insular nodular Enh	LACUNAR STROKE	AED	Complete	7	No	Tumor remission	4

							ADC hyposignal								
28	M	70	GBM, T-I, L	Su+carmustine wafer implant; RT; Ch; Cyberknife	1	Aphasia, Right hemiparesis	Left F-T focal slow abnormalities	Left capsulo-putaminal nodular hyperintensity	Left capsulo-putaminal nodular HS on b1000, no ADC hyposignal	No Enh	LACUNAR STROKE	Antiplatelets, AED	Partial (dysphasia)	90	No	Death for tumor progression	0,6
29	M	29	Gr. II Oligo, T, R	Su; RT (54 Gy)	21	Left hemiparesis, Left sensory deficit	Right T focal slow and epileptic abnormalities	n.a.	Multiple foci of diffusion restriction in right posterior deep WM	n.a.	LACUNAR STROKE	Antiplatelets, AED	Complete	14	Yes (ipsil.)	Tumor progression 1 year after 1st episode	7
30	F	38	Low grade glioma, T-I, L	RT; Ch	12	Dysarthria, Right hemiparesis, Right sensory deficit	Left F-T slow abnormalities	Left nodular periven. HS	n.a.	Left perivein. nodular Enh	LACUNAR STROKE	Antiplatelets, AED	Complete	15	Yes (ipsil.)	Tumor progression 2 years after 1st episode	4
31	M	17	Probable germinoma,	WBRT	32	Right hemiparesis, Right sensory	No abnormalities	Focal area of HS in left periventricul	Focal area of HS in left periven.	No Enh	LACUNAR STROK	Antiplatelets	Complete	10	Yes (contral.)	Tumor remission	1,5

			midline			deficit		ar WM	WM on b1000 (ADC n.a.)		E						
32	F	58	Pituitary adenoma	Su; RT	6	Left hemiparesis, Left sensory deficit	No abnormalities	Focal area of HS in right thalamus	Focal area of diffusion restriction in right thalamus	n.a.	LACUNAR STROKE	Antiplatelets, AED	Complete	14	Yes (ipsil. and contral.)	Tumor stable disease	1,2

Legend to Table 2. AED: antiepileptic drugs; Ch: chemotherapy; contral.: contralateral; Enh: enhancement; GBM: glioblastoma; Gr: grade; HS: hypersignal; ipsil.: ipsilateral; I: insular; L: left; n.a.: not available; Oligo: oligodendroglioma; PCNSL: primary central nervous system lymphoma; periven.: periventricular; R: right; RT: radiotherapy; Su: surgery; T: temporal; WBRT: whole brain radiotherapy; WM: white matter.

Table 3. "Stroke-like" events: summary of main clinical-paraclinical features, treatment and outcome in patients in the present series (n=26) and in literature (n=87).

	PRESENT SERIES (n=26)	**LITERATURE REVIEW (n=87)**
PREVIOUS TUMOR HISTORY		
Tumor type:		
Primary brain tumor	16 (62%)	62 (71%)
CNS localizations or prophylaxis in patients with systemic cancer	7 (27%)	23 (26%)
Intracranial extradural tumor	2 (8%)	2 (2%)
Other	1 (4%)	0
RT type :		
Focal RT	13 (48%) [b]	36 (53%) [c]
WBRT / CS RT	14 (52%) [b]	32 (47%) [c]
Median age at the time of RT, years (range)	37 (4-69)	31 (5-71)
Intrathecal Ch	3 (12%)	1 (1%) [c]
Systemic Ch	15 (58%)	28 (41%) [c]
CLINICAL-RADIOLOGICAL FEATURES DURING THE ACUTE EPISODE		
Median delay after RT, years (range)	10 (0.75-43)	13 (1-35)
Neurological presentation :		
Encephalopathy	13 (50%)	36 (41%)
"Stroke-like" deficits	20 (77%)	76 (87%)
Seizures	9 (35%)	55 (63%)
Headache	9 (35%)	63 (72%)
Acute MRI abnormalities	19 (73%)	75 (86%)

TREATMENT AND OUTCOME		
Steroid administration	17 (65%)	24 (28%)
Steroid dependence [a]	3 (12%)	n.a.
Full recovery	22 (85%)	69 (79%)
Recurrent episodes	16 (62%)	49 (56%)
Median FU, years (range)	3.5 (0.5-20)	1.5 (0.25-14)

Legend to Table 3. Abbreviations: - = not applicable; Ch= chemotherapy; CS= craniospinal; FU= follow-up; n.a. = not available; RT= radiotherapy; WBRT= whole brain radiotherapy. [a] Steroid-dependence is defined by neurological deterioration at steroid tapering. [b] Percentages are calculated over a total of n+1 irradiations (patient n°8 was irradiated twice). [c] Percentages are calculated over a total of 68 patients, as previous tumor treatments, including radiotherapy type, are unavailable in 19 cases.