Peri-ictal pseudoprogression in patients with brain tumor

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Recent advances in the treatment of malignant gliomas have highlighted the fact that the appearance of new contrast-enhancing lesions on magnetic resonance imaging (MRI) is not always indicative of tumor recurrence. It has been suggested that transient seizure-related MRI changes could mimic disease progression (peri-ictal pseudoprogression [PIPG]). However, the clinical and MRI features associated with this situation have not been well described. Here, we consulted the databases of 6 institutions to identify patients with brain tumor who presented during the follow-up period transient MRI lesions wrongly suggesting tumor progression in a context of epileptic seizures. Ten patients were identified. All patients but 1 were long-term survivors who had initially been treated with radiotherapy. The PIPG episode occurred after a median interval of 11 years after radiotherapy. MRI features were highly similar across patients and consisted of transient focal cortical and/or leptomeningeal enhancing lesions that erroneously suggested tumor progression. All patients improved after adjustment of their antiepileptic drugs and transient oral corticosteroids, and MRI findings were normalized 3 months after the PIPG episode. Two patients demonstrated several seizure relapses with the same clinicoradiological

pattern. After a median follow-up period of 3.5 years after the initial PIPG episode, only 1 patient presented with a tumor recurrence. In conclusion, in patients with brain tumor, especially in long-term survivors of radiotherapy, the appearance of new cortical and/or leptomeningeal contrast-enhancing lesions in a context of frequent seizures should raise the suspicion of PIPG. This phenomenon is important to recognize in order to avoid futile therapeutic escalation.

Keywords: brain tumor, epilepsy, glioma, pseudoprogression, radiotherapy.

In patients with brain tumor, the appearance of new contrast-enhancing lesions on magnetic resonance images (MRIs) frequently indicates disease progression. However, recent advances in the treatment of malignant gliomas have increased the awareness that progressive lesions on MRI are not always indicative of tumor recurrence.¹ Indeed, on early posttreatment MRI, up to one-third of patients with malignant glioma treated with temozolomide radiochemotherapy display increased edema and contrast enhancement in relation to subacute radiation effects.^{1,2} This condition, which can erroneously suggest tumor progression, has been called pseudoprogression and is an important feature to acknowledge to avoid futile therapeutic escalation.¹ Importantly, clinicians might encounter pseudoprogression not only in the early post-radiochemotherapy period, but also in other clinical situations during the follow-up of brain tumor patients,³

Received January 21, 2011; accepted April 7, 2011.

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the most emblematic being delayed radiation necrosis, which may occur decades after treatment.^{1,4}

Approximately one-half of patients with brain tumors develop seizures during the course of their illness,⁵ and the occurrence of a first seizure or the recurrence of epilepsy after prolonged seizure control is frequently associated with tumor relapse.^{6,7} However, brain tumor–related seizures might also result in transient MRI abnormalities that can incorrectly suggest tumor progression. This phenomenon, which we refer to as peri-ictal pseudoprogression (PIPG), has previously been reported in a few patients; however, its clinical and MRI features have not been well described.^{8–11} The aim of the present study was to assess the clinical and radiological features associated with PIPG to aid in the recognition of this potentially important diagnostic pitfall in neuro-oncology.

Methods

A retrospective study was performed in 6 institutions (Service de Neuro-oncologie, Hospices Civils de Lyon, Lyon, France; Department of Neuro-Oncology, Daniel de Hoed Cancer Center/Erasmus University Medical Center, Rotterdam, The Netherlands; Neuro-oncology Unit, Department of Neurology, Hôpital Central, Centre Hospitalier Universitaire de Nancy, Nancy, France; Service de Neurologie, CHU Hôpital Pasteur, Nice, France; Fédération de Neurologie Mazarin, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; and Service de Neurologie, Centre Hospitalier de Colmar,

Colmar, France) to identify patients with brain tumor who had presented with transient MRI lesions that inaccurately suggested tumor progression in a context of epileptic seizures. All types of brain tumors were considered for inclusion. We identified 10 patients with a final diagnosis of PIPG and reviewed their clinical and MRI features. The criteria used for the diagnosis of epileptic seizures were the occurrence of clinical signs of seizure activity and/or an electroencephalogram (EEG) suggestive of electrographic seizure activity. Baseline, peri-ictal, and follow-up imaging findings were independently reviewed by 2 authors (S.R. and F.D.). Baseline MRI was available in all patients except 2 (patients 1 and 5), who had computed tomography (CT) scans with contrast agent only. In the peri-ictal period, all patients underwent MRI that included fluid-attenuated inversion recovery (FLAIR) imaging or T2- and T1-weighted imaging after the administration of gadolinium contrast material. Diffusion-weighted imaging (DWI) was conducted in 4 patients and perfusion-weighted imaging (PWI) and MRI spectroscopy in 2 patients. Follow-up imaging was performed in all patients and included, at minimum, FLAIR or T2- and T1-weighted imaging after the administration of gadolinium contrast material.

Results

The baseline clinical characteristics of all patients are presented in Table 1. A total of 7 men and 3 women were included in this study. Median age at the time of

Table 1. Patients' initial characteristics

Study	Patient	Age at treatment onset (years)	Tumor characteristics		Tumor treatment	Epilepsy at diagnosis	Overall survival duration (years)
			Type	Location			
Current study	1	8	Medullo.	Cerebellum	Su; Ch; Rx	+	≥32
	2	31	Gr. II Astro.	T	Su; Rx	+	≥25
	3	46	Gr. III Oligo.	F	Su; Ch; Rx	–	≥13.3
	4	52	Gr. III Oligo.	F	Su; Rx	+	≥14
	5	48	Sing. meta.	F	Su; Rx	–	≥12
	6	44	GBM	P-O	Su; Ch; Rx	+	≥14
	7	41	Gr. II Oligo.	P	Su; Ch; Rx	+	≥11
	8	43	Gr. II Oligo.	F	Su; Ch; Rx	+	≥19
	9	35	Gr. III Oligo.	F-T	Su; Ch; Rx	+	≥8
	10	41	Gr. II Oligo.	T	–	–	≥3.5
Quan et al., 1999 ¹¹	1	25	GBM	F	Su; Ch; Rx	+	≥10
Laigle et al., 2002 ¹²	1	41	Ganglioglioma	T	–	–	na
Hormigo et al., 2004 ¹⁰	1	na	Ependy.	Post. Fossa	na	na	na
	2	na	Oligo.	T-P	na	na	na
	3	56	GBM	F	Su; Rx	na	≥8
Hattingen et al., 2006 ⁹	1	26	Gr. III Astro.	O	Su; Rx	na	≥8
Finn et al., 2007 ⁸	1	27	Glioma	O	Su; Ch; Rx	na	≥12.4
	2	na	Gr. III Astro.	P-O	Su; Ch; Rx	na	≥5
	3	na	Meningioma	P	Su; Rx	na	na

Astro. indicates Astrocytoma; Ch indicates Chemotherapy; Ependy. indicates ependymoma; F indicates frontal; GBM indicates glioblastoma; Gr. indicates grade; Medullo. indicates medulloblastoma; na indicates not available; oligo. indicates oligodendroglioma; PIPG indicates peri-ictal pseudoprogression; O indicates occipital; P indicates parietal; P-O indicates parieto-occipital; Post. Fossa indicates posterior fossa; Rx indicates radiotherapy; Sing. meta. indicates single metastasis; Su indicates surgery; T indicates temporal; – indicates no or none.

PIPG was 50 years (range, 33–65 years). In 9 patients, the PIPG occurred during the follow-up of the brain tumor, whereas it preceded the diagnosis of brain tumor in the remaining patient (patient 10). In this patient, an MRI performed after several inaugural generalized seizures revealed a right temporal infiltrative tumor with cortical and leptomeningeal contrast enhancement (Fig. 1). After seizure control, contrast enhancement disappeared, and the patient was diagnosed with a low-grade oligodendroglioma at surgery 1.5 years later. Of the 9 other patients, 3 patients (patients 2, 7, and 8) had a tumor consisting of a low-grade glioma, and 4 patients (patients 3, 4, 6, and 9) had a high-grade glioma. One patient (patient 1) had a medulloblastoma, and the final patient (patient 5) had a single brain metastasis from an unknown primary. Treatment of the tumor consisted of surgery and radiotherapy in all patients, and 6 patients also received adjuvant chemotherapy (patients 1, 3, and 6–9). Median age at treatment onset was 43 years (range, 8–52 years). Patient 4 developed a histologically proven focal radiation necrosis 3 years after radiotherapy. Patient 1 developed a right frontal localized relapse of his medulloblastoma 9 years after radiotherapy that was effectively treated with surgery and chemotherapy. Seven patients initially had partial epilepsy; however, their seizures were well controlled by antiepileptic drugs before the PIPG episode.

At the time of PIPG, all patients—except patient 10, in whom the PIPG episode revealed a low-grade glioma—were in complete remission and were long-term survivors. Indeed, in these patients, the PIPG episode

Fig. 1. Peri-ictal and follow-up T1-weighted imaging after the administration of gadolinium contrast material in patient 10. In October 2006, the patient had 3 generalized seizures, and MRI revealed a right temporal lesion with slight nodular enhancement, initially assumed to be an ischemic lesion. After the introduction of an antiepileptic drug, the control MRI showed a nonenhancing temporal lesion. The patient benefited from near total resection of this lesion in March 2008, and pathological examination of the surgical specimen showed low-grade oligodendroglioma with combined 1p/19q loss. At the most recent follow-up in March 2010, the patient was in complete remission.

occurred after a median delay of 11 years after radiotherapy (range, 3–25 years). Clinical and radiological features at the time of PIPG are presented in Table 2. Four patients (patients 1, 4, 7, and 8) demonstrated partial status epilepticus, and 5 patients presented with frequent partial seizures (patients 2, 3, 5, 6, and 9). Three patients (patients 3, 6, and 9) also had frequent subclinical epileptic discharges on the EEG. The ictal signs and/or the EEG abnormalities correlated with the topography of the MRI changes in all patients. A post-ictal focal deficit was observed in 6 patients (patients 1, 4, and 6–9) and was the main manifestation of the seizures in 3 patients (patients 6, 8, and 9). After several partial seizures, patient 9 developed a progressive severe left hemiparesis. Patient 6 showed a progressive sensory ataxia of the left arm associated with frequent brief episodes of paresthesia that were only identified as seizures when subclinical epileptic discharges were observed on the EEG. Patient 8 presented with a progressive frontal syndrome that eventually led to chemotherapy onset before a frontal partial status epilepticus was recognized.

During PIPG, MRI features were highly similar across patients. In patient 10, in whom the PIPG episode had revealed the low-grade glioma, the MRI showed a slight leptomeningeal and cortical enhancement (Fig. 1). In the 9 other patients who had been previously treated, the MRI demonstrated the appearance of new contrast-enhancing lesions. These lesions had the same cortico-leptomeningeal topography observed in patient 10 but were more marked (Fig. 2). In these patients, the contrast enhancement was adjacent to the initial site of tumor localization and, therefore, very probably within the initial radiation field (however, the radiation fields were not reviewed). T2/FLAIR sequences either did not show any new lesion or demonstrate a cortical hypersignal (patients 1, 4, 6, and 8). Four patients underwent DWI; in 2 of these patients, DWI did not show any recent abnormality, whereas in the other 2 (patients 5 and 6), it demonstrated a focal hypersignal associated with an elevated apparent diffusion coefficient suggestive of vasogenic edema. Perfusion MRI was performed in 2 patients (patients 6 and 9) and demonstrated a focal yet moderate increase in the relative cerebral blood volume. MRI spectroscopy was performed in 2 patients (patients 6 and 9) and demonstrated a moderate increase of the choline/creatine ratio in 1 patient (patient 6) and no increase in the other patient (patient 9). Lastly, although the 3 patients in whom the enhancing lesions were the most extensive suffered from either partial status epilepticus (patients 1 and 4) or subcontinuous subclinical epileptic discharge (patient 9) (Fig. 2), no formal correlation could be established between the radiological features and the intensity or duration of the epileptic activity.

The clinical situation progressively improved following the introduction or adjustment of antiepileptic drugs in all patients. Seven patients also received steroids. The post-ictal deficit usually persisted for several days to weeks before improvement. In addition, in accordance

Table 2. Clinico-radiological features of peri-ictal pseudoprogression (PIPG)

Study	Patient #	Age at PIPG	Delay before PIPG	Tumor outcome before PIPG	Clinical features	Clinical and/or subclinical discharges on EEG	Post-ictal deficit	MRI changes					Treatment	Post-PIPG follow-up (years)
								Gd-T1	T2/FLAIR	DWI/ADC	MRS	Perfusion		
Current study	1	33	25	Complete Rem.	Part. SE	+	+	Lept. + Cort.	Cort. HS	na	na	na	AED	7
	2	54	23	Complete Rem.	Part. seiz.	–	–	Lept. + Cort.	NI	na	na	na	AED	2
	3	59	13	Complete Rem.	Part. seiz.	+	–	Lept. + Cort.	NI	na	na	na	AED	0.25
	4	65	13	Complete Rem.	Part. SE	+	+	Lept. + Cort.	Cort. HS	na	na	na	AED; CS	1
	5	59	11	Complete Rem.	Part. seiz.	–	–	Lept. + Cort.	NI	Incr./Incr.	na	na	AED; CS	1
	6	52	8	Complete Rem.	Part. seiz.	+	+	Lept. + Cort.	Cort. HS	Incr./Incr.	NI	rCBV incr.	AED; CS	6
	7	48	8	Complete Rem.	Part. SE	+	+	Lept. + Cort.	NI	na	na	na	AED; CS	3
	8	48	5	Complete Rem.	Part. SE	+	+	Lept. + Cort.	Cort. HS	NI	na	na	AED; CS	14
	9	38	3	Complete Rem.	Part. seiz.	+	+	Lept. + Cort.	NI	NI	Chol/creat incr.	rCBV incr.	AED; CS	5
	10	41	0	Complete Rem.	Gen. Seiz.	–	–	Lept. + Cort.	Na	na	na	na	AED	3,5
Quan et al., 1999	1	35	10	Complete Rem.	Part. seiz.	–	+	Lept. + Cort.	Cort. HS	na	NI	na	AED	–
Laigle et al., 2002	1	41	0	Complete Rem.	Gen. Seiz.	–	–	Lept. + Cort.	Na	na	na	na	AED; Su	–
Hormigo et al., 2004	1	62	na	Complete Rem.	NCSE	+	+	Lept. + Cort.	Cort. HS	NI	na	na	AED	0.4
	2	39	na	Complete Rem.	NCSE	+	+	Lept. + Cort.	Cort. HS	Incr./–	na	na	AED	2
	3	62	6	Complete Rem.	NCSE	+	+	Lept. + Cort.	Cort. HS	Incr./–	na	na	AED	2
Hattingen et al., 2006	1	38	12	Complete Rem.	Part. seiz.	+	+	Lept. + Cort.	Cort. HS	Incr./Decr.	Chol/creat incr.	na	AED	0.4
Finn et al., 2007	1	31	4	Complete Rem.	Gen. Seiz.	na	na	Lept. + Cort.	Na	na	na	na	AED	1
	2	43	na	na	Part. seiz.	na	na	Lept. + Cort.	Cort. HS	na	na	na	AED	na
	3	56	na	na	Part. seiz.	na	+	Lept. + Cort.	Cort. HS	na	na	na	AED	0.08

ADC indicates apparent diffusion coefficient; AED indicates antiepileptic drugs; Cort. indicates cortical; CS indicates corticosteroids; Decr. indicates decreased; DWI indicates diffusion-weighted imaging; Gd indicates gadolinium; Gen seiz. indicates generalized seizure; Incr. indicates increased; Lepto. indicates leptomeningeal; NCSE indicates nonconvulsive status epilepticus; na indicates not informed; NI indicates no abnormality; Part. SE indicates partial status epilepticus; Part. seiz. indicates partial seizures; PIPG indicates peri-ictal pseudoprogression; Rem. indicates remission; – indicates none, + indicates yes.

Fig. 2. Peri-ictal and follow-up T1-weighted imaging after administration of gadolinium contrast material in patients 1–9.

with the initial suspicion of tumor relapse, patient 8 received a single cycle of procarbazine, CCNU, and vincristine (PCV) chemotherapy. However, because this patient was still in complete remission 14 years later, the hypothesis that it was simply a response to PCV seems very unlikely. All patients showed normalized MRI findings within 3 months after the PIPG episode. The delay in MRI finding normalization varied from 1 to 3 months. Because most patients did not undergo monthly follow-up MRI, we cannot exclude the possibility that radiological normalization might have occurred earlier.

Interestingly, 2 patients demonstrated PIPG relapses (patient 6, 1 relapse; and patient 9, 3 relapses). The radiological features remained highly similar across these PIPG episodes (Fig. 3). Interestingly, in patient 9, the last episode was diagnosed on a systematic MRI while the patient was still asymptomatic. This MRI showed the reappearance of the abnormalities observed earlier during PIPG, leading to a repeat of the EEG that revealed subclinical epileptic discharges.

At last follow-up, after a median period of 3.5 years (range, 0.25–14 years) after the initial PIPG episode, only 1 patient presented with a tumor recurrence (patient 4). In this patient, a follow-up MRI demonstrated a new cortical enhancing lesion 9 months after the PIPG episode that was considered true tumor progression and successfully treated with PCV chemotherapy.

Discussion

The analysis of our 10 patients together with the analysis of 9 previously reported cases highlights 2 main characteristics that may aid the recognition of PIPG. First, PIPG

seems to occur preferentially among long-term survivors who have undergone radiotherapy. The relationship between PIPG and prolonged survival after radiotherapy has not been previously recognized but is consistent with earlier reports (Tables 1 and 2). Indeed, all previously reported cases of PIPG for which the information regarding initial treatment and survival was available also received radiotherapy ($n = 6$) and had a prolonged survival ($n = 4$).^{8–11} However, as previously suggested¹² and observed in one of our patients (patient 10), PIPG can also sometimes occur in untreated patients, in whom it can incorrectly suggest a higher-grade glioma.

Second, our study shows that PIPG MRI features are stereotyped and easy to recognize. They consist of focal cortical and/or leptomeningeal enhancing lesions, suggestive of extensive blood-brain barrier disruption. These MRI changes are similar to those reported in previous PIPG cases.^{8–11} Specifically, all 6 previously described patients with brain tumor for whom peri-ictal MRIs were available also demonstrated similar cortical enhancements.^{8–11} T2-weighted sequences and DWI are inconstantly modified. MRI spectroscopy might either show a normal profile or a moderate choline/creatinine ratio increase, erroneously suggesting tumor recurrence.^{9,11} Perfusion imaging may also be misleading. In the 2 patients in whom it was performed, perfusion imaging demonstrated a moderate rCBV increase, suggestive of tumor recurrence. Similarly, a potentially misleading hypermetabolic activity can be observed on [¹⁸F]FDG PET imaging.¹⁰ However, the number of patients who underwent diffusion, perfusion imaging, or MRI spectroscopy is too small to allow definitive conclusions regarding the use of these techniques for the diagnosis of PIPG. Overall, it appears that in the context of seizures, the morphology of the contrast

Fig. 3. Examples of peri-ictal pseudoprogression (PIPG) relapse in patients 6 and 9 (T1-weighted imaging after administration of gadolinium contrast material). Patient 6 was treated with surgery, radiotherapy, and adjuvant chemotherapy for a right-side parietal glioblastoma. Eight years after radiotherapy, he presented with a first PIPG episode, which was resolved with oral corticosteroids and an adjustment of his antiepileptic drugs. A second episode of PIPG was observed 5 years later and was treated by antiepileptic drug adjustment only. At the most recent follow-up in October 2010, the patient was in complete remission. Patient 9 was treated with surgery, radiotherapy, and adjuvant chemotherapy for a right fronto-temporal high-grade oligodendroglioma. Three years after radiotherapy, he presented a first episode of PIPG, which resolved with adjustment of antiepileptic drugs and oral corticosteroids. Thereafter, he demonstrated 2 other PIPG episodes, including one related to subclinical epileptic discharges only. At the most recent follow-up visit in October 2010, he was still in complete remission.

enhancement—namely, its cortico-leptomeningeal location—is the most stereotyped imaging feature that should suggest the possibility of PIPG. Importantly, the appearance of these MRI abnormalities should precipitate the performance of an EEG even in the absence of a clear history of seizures given that the clinical manifestation of seizures may be misleading or absent (patients 6 and 8 presented with a progressive neurological deficit, and in patient 9, the last episode was diagnosed by systematic MRI).

Importantly, these MRI features are different from those usually observed in patients without brain tumors. Transient peri-ictal MRI changes have been described in epileptic patients for both partial^{13,14} and generalised epilepsy,¹⁵ irrespective of the underlying pathology.^{13,14,16,17} These MRI changes are usually observed in patients with status epilepticus and consist mostly of focal cortical swelling and restricted diffusion related to both cytotoxic and vasogenic edema.^{14,15,17,18} Leptomeningeal enhancements and/or cortical enhancements can be observed but remain infrequent,^{13,15,18,19} and when they occur, they usually resemble those

observed in patient 10^{13,15,18,19} and are less marked and less extensive than those observed in previously irradiated patients.

Although the formal incidence of PIPG could not be extrapolated from the current study, especially in the population of post-radiotherapy long-term survivors, PIPG remains a rare entity. As a matter of fact, only 10 patients could retrospectively be identified in 6 health care centers over a period of ~20 years. By contrast, focal radionecrosis has been reported in 3%–24% of patients treated by radiotherapy¹ (Table 3).

Importantly, PIPG was not necessarily limited to a single episode, and as reported previously,^{8–11} 2 patients had PIPG relapses. Given the frequent difficulties in achieving seizure freedom in patients with brain tumor who have epilepsy,⁵ the recurrence of PIPG might not be surprising. However, this observation highlights the risk of repeated futile therapeutic escalations and the related side effects in patients with several episodes of PIPG that would not have been otherwise recognised.

The mechanisms underlying the MRI changes in PIPG remain undetermined, and we can only speculate

Table 3. Clinical and radiological features of peri-ictal pseudoprogression (PIPG), SMART syndrome, and focal radionecrosis

Variable	PIPG ^{Present study, 8–11}	SMART syndrome ^{20–25}	Focal radionecrosis ^{1,4}
Incidence	Rare	Rare	3%–24%
Typical delay of occurrence after radiotherapy	Long-term survivors (> 10 years)	Long-term survivors (> 10 years)	During the first 2 years but occurrence after decades described
Risk factors	Unknown	Unknown	Total radiation dose, dose of each fraction, irradiated volume
Clinical symptoms	Seizures Headaches Others	Rare (if present mostly generalized seizures) Constant, migraine-like Stroke-like deficits	Frequent
Typical MRI characteristics	Constant, mostly partial seizures, including subclinical epileptic discharges No Post-ictal deficits Focal cortical and/or leptomeningeal enhancing lesions, suggestive of extensive blood-brain barrier disruption Cortical and/or leptomeningeal, sparing the white matter	Diffuse unilateral cortical gadolinium enhancement of the cerebral gyri Cortical and/or leptomeningeal, often affecting the parieto-occipital cortex, sparing the white matter	Frequent, intracranial hypertension Focal neurological deficits Contrast-enhancing mass on T1-weighted imaging with gadolinium White matter, frequently located within the periventricular white matter
Treatment	Typical location Mass effect	No antiepileptic drug adjustment with or without corticosteroids	Yes Corticosteroids, surgery, bevacizumab
Clinical course	Constant full recovery within weeks to few months; relapses possible	Symptomatic treatment of headaches Constant full recovery within days to few weeks; relapses possible	Highly variable, from full recovery to death

on the basis of our results and other data from the literature. The clinico-radiological features of PIPG and its rapid improvement indicate that it does not correspond to focal brain radiation necrosis.^{1,4} Radiation necrosis lesions most often predominate in the white matter and are associated with vasogenic edema.^{1,4} In epileptic patients, peri-ictal MRI findings have mostly been related to increased neuronal activity and the associated metabolic and vascular responses.^{14,17} Given the long-term radiation-induced vascular changes,⁴ it might be speculated that the vascular response to seizures might be altered in irradiated patients, promoting the extensive seizure-related blood-brain barrier disruption observed in our patients. On the other hand, one cannot exclude the possibility that long-term radiation-induced vascular changes might be the cause rather than the consequence of the seizures. It has been suggested that post-radiation cortical vasculopathy might precipitate the occurrence of nonepileptic reversible neurological symptoms, which have been described as the SMART syndrome (stroke-like migraine attacks after radiation therapy).^{20–24} Interestingly, these symptoms are associated with transient dramatic cortical gadolinium enhancement of the affected cerebral hemisphere with an aspect similar to that observed in PIPG.^{20–25} Accordingly, it might be speculated that SMART and PIPG could be the expression of the same phenomenon, which might be related to the long-term vascular alterations following brain radiotherapy. However, the clinical presentation in patients with PIPG is clearly different from the presentation reported in patients with SMART syndrome, as highlighted by the fact that none of the patients examined in this study presented with acute headaches or a stroke-like deficit (Table 3). Moreover, patients with SMART syndrome typically do not present with classical seizure activity. Furthermore, although both SMART syndrome and PIPG occur in long-term survivors after radiotherapy, the age at radiotherapy onset seems to be different. Indeed, median age at radiotherapy onset was 15.5 years in the 19 reported cases of SMART syndrome, compared with 41 years in the reported PIPG cases, including our series ($P = .001$, by Mann-Whitney U test). Finally, it has been suggested that the transient MRI abnormalities observed in SMART syndrome might predominantly affect the parieto-occipital cortex,²⁵ whereas PIPG has been observed in all cortical regions.

In conclusion, the results from this study indicate that in patients with brain tumor, especially in long-term survivors treated with radiotherapy, the appearance of new cortical and/or leptomeningeal contrast-enhancing lesions in a context of seizures should raise the suspicion of PIPG. We hypothesize that this phenomenon might develop in relation to a post-irradiation cortical vasculopathy.

Acknowledgments

The authors received no specific funding for this study.

None of the authors reports disclosures.

References

1. Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ. Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. *Lancet Oncol*. 2008;9:453–461.
2. Brandes AA, Franceschi E, Tosoni A, et al. MGMT promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. *J Clin Oncol*. 2008;26:2192–197.
3. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol*. 2010;28:1963–1972.
4. Soussain C, Ricard D, Fike JR, Mazeran JJ, Psimaras D, Delattre JY. CNS complications of radiotherapy and chemotherapy. *Lancet*. 2009;374:1639–1651.
5. Ruda R, Trevisan E, Soffietti R. Epilepsy and brain tumors. *Curr Opin Oncol*. 2010;22:611–620.
6. Chaichana KL, Parker SL, Olivi A, Quinones-Hinojosa A. Long-term seizure outcomes in adult patients undergoing primary resection of malignant brain astrocytomas: clinical article. *J Neurosurg*. 2009;111:282–292.
7. Hwang SL, Lin CL, Lee KS, et al. Factors influencing seizures in adult patients with supratentorial astrocytic tumors. *Acta Neurochir (Wien)*. 2004;146:589–594: discussion 594.
8. Finn MA, Blumenthal DT, Salzman KL, Jensen RL. Transient postictal MRI changes in patients with brain tumors may mimic disease progression. *Surg Neurol*. 2007;67:246–250; discussion 250.
9. Hattingen E, Franz K, Pilatus U, Weidauer S, Lanfermann H. Postictal spectroscopy and imaging findings mimicking brain tumor recurrence. *J Magn Reson Imaging*. 2006;24:226–230.
10. Hormigo A, Liberato B, Lis E, DeAngelis LM. Nonconvulsive status epilepticus in patients with cancer: imaging abnormalities. *Arch Neurol*. 2004;61:362–365.
11. Quan D, Hackney DB, Pruitt AA, Lenkinski RE, Cecil KM. Transient MRI enhancement in a patient with seizures and previously resected glioma: use of MRS. *Neurology*. 1999;53:211–213.
12. Laigle F, Martin-Duverneuil N, Carpentier A, Hoang-Xuan K, Delattre JY. Seizure-related contrast enhancement of a ganglioglioma. *Neurology*. 2002;58:1538.
13. Lansberg MG, O'Brien MW, Norbash AM, Moseley ME, Morrell M, Albers GW. MRI abnormalities associated with partial status epilepticus. *Neurology*. 1999;52:1021–1027.
14. Szabo K, Poepel A, Pohlmann-Eden B, et al. Diffusion-weighted and perfusion MRI demonstrates parenchymal changes in complex partial status epilepticus. *Brain*. 2005;128:1369–1376.
15. Kim JA, Chung JJ, Yoon PH, et al. Transient MR signal changes in patients with generalized tonicoclonic seizure or status epilepticus: perictal diffusion-weighted imaging. *AJNR Am J Neuroradiol*. 2001;22:1149–1160.
16. Briellmann RS, Wellard RM, Jackson GD. Seizure-associated abnormalities in epilepsy: evidence from MR imaging. *Epilepsia*. 2005;46:760–766.
17. Cole AJ. Status epilepticus and perictal imaging. *Epilepsia*. 2004;45(Suppl 4):72–77.
18. Goyal MK, Sinha S, Ravishankar S, Shivshankar JJ. Peri-ictal signal changes in seven patients with status epilepticus: interesting MRI observations. *Neuroradiology*. 2009;51:151–161.
19. Raghavendra S, Ashalatha R, Krishnamoorthy T, Kesavadas C, Thomas SV, Radhakrishnan K. Reversible perictal MRI abnormalities: clinical correlates and long-term outcome in 12 patients. *Epilepsy Res*. 2007;73:129–136.
20. Partap S, Walker M, Longstreth WT, Jr, Spence AM. Prolonged but reversible migraine-like episodes long after cranial irradiation. *Neurology*. 2006;66:1105–1107.
21. Murthy SN, Cohen ME. Pseudomigraine with prolonged aphasia in a child with cranial irradiation for medulloblastoma. *J Child Neurol*. 2002;17:134–138.
22. Bartleson JD, Krecke KN, O'Neill BP, Brown PD. Reversible, stroke-like migraine attacks in patients with previous radiation therapy. *Neuro Oncol*. 2003;5:121–127.
23. Black DF, Bartleson JD, Bell ML, Lachance DH. SMART: stroke-like migraine attacks after radiation therapy. *Cephalalgia*. 2006;26:1137–1142.
24. Shuper A, Packer RJ, Vezina LG, Nicholson HS, Lafond D. 'Complicated migraine-like episodes' in children following cranial irradiation and chemotherapy. *Neurology*. 1995;45:1837–1840.
25. Kerklaan JP, Lycklama A, Nijeholt GJ, et al. SMART syndrome: a late reversible complication after radiation therapy for brain tumors. *J Neurol*. 2011;258(6):1098–1104.