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Solitary Cerebral Metastases *vs*. High-grade Gliomas: Usefulness of Two MRI Signs in the Differential Diagnosis

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Abstract. *Background/Aim: The differentiation between cerebral metastases (CM) and high-grade gliomas (HGG) can be difficult on magnetic resonance imaging (MRI). The aim of this study was to evaluate the usefulness of searching two MRI signs (signal alteration in the adjacent cortex, SAAC, and peripheral rim sign, PRS), in order to distinguish between these entities. Patients and Methods: A total of 61 patients were retrospectively enrolled (28 HGG, 33 CM). Fluid Attenuated Inversion Recovery (FLAIR) sequences were used to assess SAAC and contrast-enhanced T1-weighted sequences for PRS. Results: A positive SAAC sign was present in 61% of HGG, and 12% of CM. Conversely, in SAAC-negative lesions, PRS was observed in 78% of CM and in 32% of HGG. Their association had a higher frequency in HGG than in the CM group (21 vs. 3%). Conclusion: While SAAC is specific for HGG and PRS, in the absence of SAAC, is relatively specific for CMs, their combined presence is highly suggestive of HGG.*

The differential diagnosis between cerebral metastases (CMs) and high-grade gliomas (HGGs) is essential for prognostic evaluation and therapeutic planning. In fact, patients with HGGs more often require neurosurgical resection as an initial approach (1), while CMs are variably treated with either neurosurgical procedure, chemotherapy or immunotherapy, or irradiation, on the basis of primitive tumour and systemic staging (2).

CMs and HGGs are detected as solitary lesions in 50% and 90% of the cases, respectively (3, 4). When they present as solitary, solid, contrast-enhancing lesions, the differential diagnosis may, sometimes, be difficult using magnetic resonance imaging (MRI), even with advanced techniques such as diffusion tensor, spectroscopy and perfusion imaging (5-14). Moreover, the routine use of these advanced techniques may be limited by operative conditions, like the availability of optimized acquisition protocols and elaboration software, and by the variable experience of radiologists and neuroradiologists in their interpretation (15, 16).

While in some cases clinical history is helpful for formulating the correct diagnosis, neurosurgery and pathology are still often used to reach a definitive diagnosis, as CMs and HGGs may share similar imaging features (7-9). Based on the fact that HGG cells very early infiltrate the surrounding brain tissue (17), the signal alteration in the cortex adjacent to a gadolinium-enhancing lesion (signal alteration in adjacent cortex, SAAC) has been proposed as a useful conventional MRI finding on unenhanced fluid attenuated inversion recovery (FLAIR) T2-weighted (T2w) sequences (17-21).

On the other hand, a recent study on the differential diagnosis between intramedullary spinal cord lesions showed that metastases were more frequently associated with a peripheral rim of higher gadolinium-enhancement, i.e. the peripheral rim sign (PRS), on T1-weighted (T1w) sequences (18). For brain metastases, the presence of this imaging finding has not been assessed, nor has the combination of PRS and SAAC been previously investigated.

Therefore, the purpose of this study was to assess the diagnostic performance of SAAC and PRS, individually and together, in the differential diagnosis between CMs and HGGs presenting as solitary, solid gadolinium-enhancing lesions.

Patients and Methods

Among the patients referred to our Institution for surgical removal of a primary or secondary brain tumor, 61 adult patients (34 males and 27 females; age range=37-84 years) affected by 33 CM (primary cancer: lung=17, breast=9, colon=3, bladder=1, kidney=1, and uterus cervix=1) and 28 HGG (24 grade IV and 4 grade III)

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were selected. Inclusion criteria required that CMs and HGGs were evident as a single, supratentorial, solid, gadolinium-enhancing lesion, as well as the availability of pathological analysis. Exclusion criteria were: infratentorial CMs and HGGs, the presence of cystic and/or necrotic areas within the lesion, or the inability to obtain an adequate MRI quality, due to excessive movement artefacts.

All MRI studies were performed at the Unit of Neuroradiology of our Institution on the same 1.5 T scanner (Signa EXCITE, General Electric, Milwaukee, WI, USA) provided with 8-channel dedicated coil, using conventional FLAIR-T2w sequences (TE: 80, TR: 8000, inversion time: 2000, frequency: 256, phase: 224, thickness: 5.0 mm, interval: 1.5 m) and FLAIR-T1w (TE 9, TR 2100, TI 700, frequency 320, phase 256, thickness mm 5, interval 1.5 mm) or SPGR-T1w (TE 8.2, Flip Angle 20°, frequency 320, phase 224, thickness 1.4 mm) sequences obtained before and after intravenous (i.v.) administration of gadolinium (Gadobutrol, Gadovist, Bayer-Schering Pharma, Berlin, Germany) at a dose of 0.1 mmol/kg. In particular, FLAIR-T1w was used in 49 cases (28 CM and 21 HGG) and SPGR-T1w in the remaining 12 (5 CM and 7 HGG). Informed consent was previously obtained from all individual participants included in the study.

Two neuroradiologists (CFM and GE), both with over 10 years of neuroradiological experience, assessed in consensus the presence of SAAC and PRS on unenhanced T2-FLAIR and axial and coronal gadolinium-enhanced T1w MR images, blind to both clinical history and histopathologic diagnosis of the patients.

SAAC was defined as the presence of a non-gadolinium-enhancing signal alteration in the FLAIR T2w image located in the cortex adjacent to a gadolinium-enhancing lesion (16-20) (Figure 1). PRS was defined as a complete or partial (covering >2/3 of lesion margin), clear-cut peripheral rim of gadolinium-enhancement, more intense than the remaining lesion border (Figure 2).

The chi-square test was used to assess the relationship between the two signs, HGG and CMs. A *p*-value equal or inferior to 0.05 was considered as statistically significant. Then, based on 2×2 contingency tables, diagnostic accuracy parameters of SAAC, PRS and their combination were computed. In particular, sensitivity, specificity, positive and negative likelihood ratio, positive and negative predictive value and overall accuracy were calculated. All analyses were conducted with a dedicated software (RStudio http://www.rstudio.com).

Results

The distribution of SAAC and PRS in HGGs and CMs is shown in Table I, while Table II presents the corresponding measures of diagnostic performance. In particular, SAAC was evident in 17 out of 28 HGGs (60.7%) and in 4 out of 33 CMs (12.1%), while PRS was observed in 26 out of 33 CMs (78.8%) and in 9 out of 28 HGGs (32.1%). Two HGGs (7%) and three CMs (9%) did not show any SAAC nor PRS.

The Chi-square test showed a significant association between SAAC and HGG ($p<0.001$) and PRS and CMs ($p<0.001$). SAAC sensitivity for HGG was 60.7%, with a specificity of 87.9% (accuracy: 75.4%), while PRS sensitivity for CMs was of 78.8%, with a specificity of 67.9% (accuracy: 73.8%). SAAC and PRS were associated in 1 out of 33 CMs, and in 6 out of 28 HGGs. In the HGG group, the association of SAAC and PRS reached a specificity of 97.0% and a positive predictive value of 85.7%, but with a sensitivity of 21.4%, and thus a low accuracy (62.3%).

Table I. *Prevalence of peripheral rim sign and signal alteration in the adjacent cortex in high-grade gliomas and cerebral metastases.*

	SAAC	PRS	SAAC and PRS
HGGs (n= 28)	17 (60.7%)	9 (32.1%)	6 (21.4%)
CMs (n=33)	4 (12.1%)	26 (78.8%)	1 (3.0%)

SAAC: Signal alteration in the adjacent cortex; PRS: peripheral rim sign; HGGs: high-grade gliomas; CMs: cerebral metastases.

Table II. *Measures of diagnostic performance for the evaluated MRI signs in high grade gliomas and metastasis.*

	SAAC	PRS	SAAC and PRS
Sensitivity	60.7%	78.8%	21.4%
Specificity	87.9%	67.9%	97.0%
Positive likelihood ratio	5.01	2.45	7.07
Negative likelihood ratio	0.45	0.31	0.81
Positive predictive value	80.9%	74.3%	85.7%
Negative predictive value	72.5%	73.1%	59.3%
Accuracy	75.4%	73.8%	62.3%

SAAC: Signal alteration in the adjacent cortex; PRS: peripheral rim sign.

Discussion

We evaluated the possibility of increasing the diagnostic power of conventional MRI in the differential diagnosis between CMs and HGGs and found that SAAC is indicative of HGG, PRS - in absence of SAAC- is relatively specific for CMs, and that their combined presence is highly suggestive of HGG.

While the value of SAAC and PRS has been previously assessed in this differential diagnosis (18-20), this is the first study evaluating their combined accuracy. Our results show that in case of a solitary, solid, gadolinium-enhancing lesion of uncertain origin, first the FLAIR T2w images should be closely searched for the SAAC sign, that would indicate the presence of HGG, as they have also been reported previously (19, 20). Then, if no SAAC is found, the presence of PRS may be assessed in the contrast-enhanced T1w images, that would point toward the metastatic nature of the lesion.

In unenhanced FLAIR T2w sequences, the signal alteration in the adjacent cortex seems to be relatively more specific, while not particularly sensitive, for HGGs rather than CMs. Tang *et al.* (19) observed a specificity of 91% and a sensitivity of 44%, while Muccio *et al.* (20) reported,

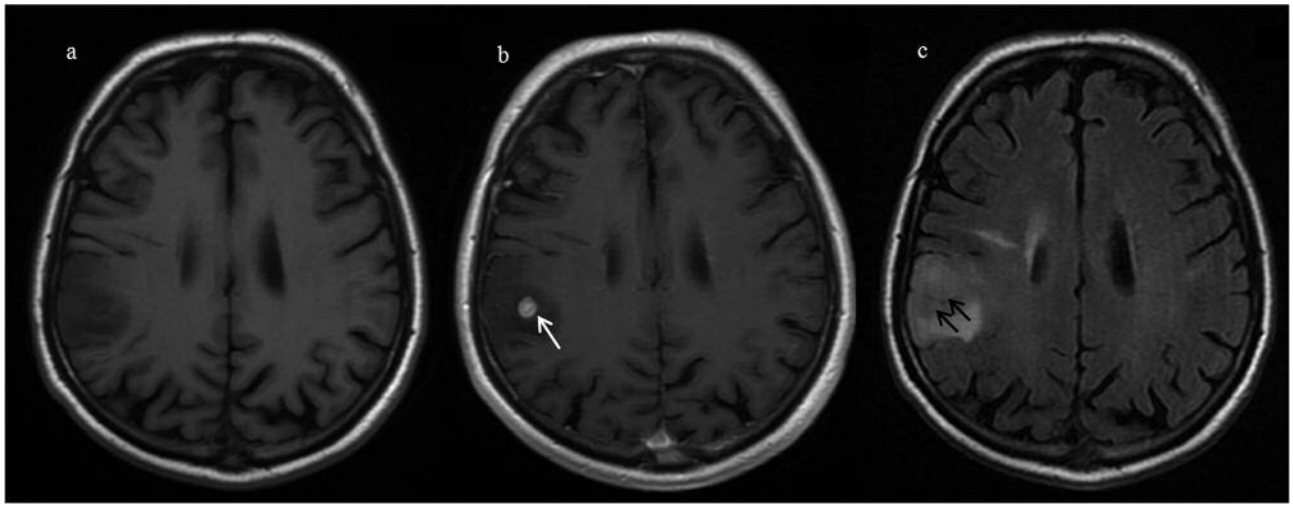

Figure 1. *Glioblastoma. Axial FLAIR T1-weighted (a), contrast-enhanced FLAIR T1-weighted (b) and unenhanced FLAIR T2-weighted images. This contrast-enhancing lesion shows a peripheral thin rim of more intense enhancement (white arrow in b), associated with high signal intensity of the adjacent cortex (SAAC) on the unenhanced FLAIR T2- weighted axial image (black arrows in c), i.e. the sign of involvement of the adjacent brain.*

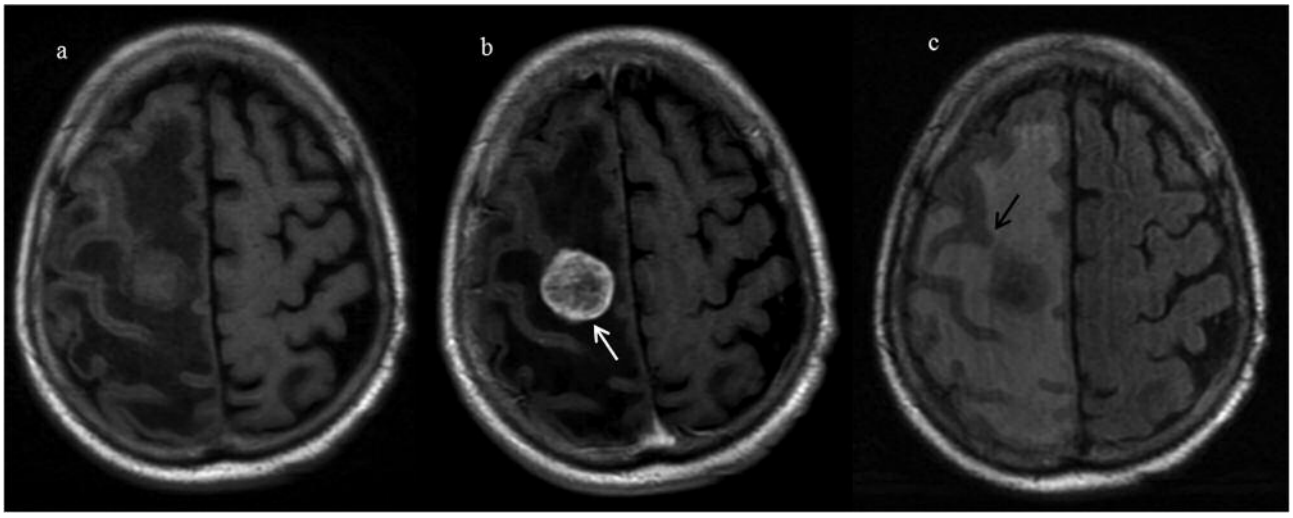

Figure 2. *Cerebral metastasis from colon carcinoma. Axial FLAIR T1-weighted (a), contrast-enhanced FLAIR T1-weighted (b) and unenhanced FLAIR T2-weighted images (c). Note the peripheral rim sign (white arrow) on gadolinium-enhanced T1-weighted FLAIR image (b), i.e. a thin rim of more intense enhancement on the outer border of the enhancing lesion. Unenhanced FLAIR T2-weighted axial image (c) does not show signal alteration (black arrow) in the brain cortex adjacent to the area of contrast-enhancement (b).*

in a larger population, a specificity of 88% and a sensitivity of 67,7%. In HGGs, tumour cells infiltrate brain tissue beyond the neoplastic margin (17), thus, gadolinium-enhancement does not coincide with the boundaries of infiltration margin, and should not be used to represent the neoplastic extension. Signal alteration in the unenhanced FLAIR-T2w sequences suggests the presence of tumour infiltration, and is, therefore, more indicative of HGGs than of CMs, even when observed in association with PRS. In fact, vasogenic edema preferentially involves white matter and largely spares gray matter (19); therefore, when a signal intensity change is found within the cortex in proximity to a subcortical lesion, this is likely due to microscopic neoplastic infiltration of the peritumoral edematous region. Even when associated with PRS, SAAC was far more frequent in HGGs (21%) than in CMs (3%).

Recently, Rykken *et al*. (18) demonstrated the usefulness of PRS in gadolinium-enhanced T1w sequences for the

differential diagnosis between intramedullary spinal cord metastases and primary solid gadolinium-enhancing lesions; an evaluation not yet performed on brain metastases so far. In our population, PRS was more frequently observed in CMs (26 out of 33) than in HGGs (9 out of 28), this difference being statistically significant at Fisher Exact Test.

Unlike in HGG, the brain areas surrounding CMs comprise predominantly vasogenic edema, without significant brain infiltration, and thus the lesion borders may appear more defined and inscribed in the gadolinium-enhancing area. This would explain the observation of PRS following gadolinium injection, while the central part of the lesion appears less enhancing. However, no histopathologic correlates of the peripheral rim sign have been identified, including no evidence for a tumor capsule (18). Moreover, the non-negligible evidence of PRS in HGG (32% as the only sign, 21% with a concomitant SAAC sign) suggests that this may represent an imaging finding not related to a specific pathologic process.

The assessment of PRS and SAAC is a fast procedure, easily feasible in a good quality conventional MRI morphologic study. When systematically performed, this assessment would improve the possibility of differentiating CMs from HGGs, even when more sophisticated and advanced diagnostic MR techniques are not available.

Both T1w SPGR and fast FLAIR gadolinium-enhanced images are used in daily practice. The assessment of both readers was qualitative regarding the evidence of PRS and SAAC signs. In gadolinium-enhanced SPGR images, flow related artifacts have been found to be significantly reduced when compared to Spin Echo images (22, 23). Despite slightly increased imaging artifacts (which, however, do not interfere with image interpretation) and longer acquisition time, gadolinium-enhanced T1w-FLAIR imaging provides good lesion conspicuity and overall image contrast (24-29). At 3T, various 3D MRI sequences are tested for the detection of brain metastases (30, 31).

While showing encouraging results, the present study is limited by its retrospective nature. A more robust validation of our approach would require a prospective analysis, involving a higher number of patients. Additionally, it may be useful to compare different gadolinium-enhanced T1w sequences at both 1.5T and 3T. Finally, as in the case of intramedullary spinal cord masses (18), future work should include dedicated correlation between neuroradiology, surgery, and histopathologic analysis of microscopic findings at the tumor margins. Neurosurgeons attempting to remove brain tumors encounter various degrees of resectability and it would be interesting to analyse whether the rim sign predicts the presence of a cleavage plane and, in turn, an easier, more complete resection.

Conclusion

In conclusion, our study suggests that, in case of a solitary, solid, gadolinium-enhancing lesion, the observation of SAAC is quite specific for HGG. The presence of SAAC is highly suggestive of HGG, even when in combination with PRS. When no SAAC is found, the presence of PRS is a more frequent and relatively specific sign for CMs than for HGGs.

Conflicts of Interest

The Authors declare that there is no conflict of interest.

Authors' Contributions

CFM conceived and designed the study and wrote the paper; ET contributed data tools and wrote the paper; LU and RC collected the data and performed the analysis; GE designed the study; FC participated to the design and coordination and helped to draft the manuscript.

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