Reverse Enhancement of Hemorrhagic Brain Lesions on Postcontrast MR: Detection with Digital Image Subtraction

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PURPOSE: To investigate the decrease in signal intensity on T1-weighted MR images of some hemorrhagic intracranial lesions after administration of contrast material. **METHODS:** Postprocessing digital image subtraction was performed in 16 MR studies (13 patients) of lesions that showed hyperintensity on noncontrast T1-weighted images. Repetition time and echo time were identical for all precontrast and postcontrast studies. Regions of interest were measured in each lesion, contralateral white matter, and background (before and after contrast enhancement). **RESULTS:** In six of 16 MR studies, a significant net decrease in signal intensity was seen within the hemorrhagic lesion after contrast enhancement (reverse enhancement). All the lesions were hematomas within residual or recurrent malignant tumors. **CONCLUSIONS:** Digital image subtraction confirms the existence of reverse enhancement. This phenomenon is due to the combined T2-shortening effects of two paramagnetic substances, methemoglobin and gadolinium, which cause the signal reduction produced by the T2 effects to occur at lower concentrations of gadolinium.

Index terms: Brain, magnetic resonance; Cerebral hemorrhage; Magnetic resonance, contrast enhancement

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Gadolinium-containing contrast agents shorten T1 relaxation time in tissues in which they accumulate, resulting in high signal intensity on T1-weighted magnetic resonance (MR) images (1). In high concentrations, these contrast agents may also result in T2 shortening (2). The presence of hyperintense subacute hemorrhage on T1-weighted images can obscure contrast enhancement in or around lesions. To overcome this problem, a simple digital subtraction technique may be used to remove effectively the subacute hemorrhagic component from the contrast-enhanced regions (3).

The apparent decrease in signal intensity on T1-weighted images seen in some lesions after intravenous administration of contrast material has been thought to be artifactual (4, 5). We present six cases of "reverse" lesional enhancement confirmed by digital subtraction and region-of-interest (ROI) measurements in MR studies performed with identical parameters and explain this observation in terms of the combined relaxation effects of methemoglobin and gadolinium.

Materials and Methods

Digital image subtraction was performed in 16 studies from 13 patients (eight male, five female; 10 to 69 years old). Cases were selected for the presence of hyperintense subacute hemorrhage in the area of interest on T1-weighted images. Diagnostic and imaging data are presented in Table 1. The subtraction technique was set to accept negative pixels.

All MR imaging studies were performed on a 1.5-T scanner using 0.1 mmol/kg of gadopentetate dimeglumine or gadoteridol. Each study included noncontrast and contrast-enhanced T1-weighted images with parameters of 450–550/11–19 (repetition time/echo time). In each case, repetition time, echo time, section thickness and location, and transmit/receive attenuation were identical

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TABLE 1: Hemorrhagic lesions for which digital subtraction images were obtained

Case	Age, y/Sex	Diagnosis	Enhancement Pattern	Reverse Enhancement?	Time Since Surgery
1	69/F	Glioblastoma*	Nodular	Yes	15 d
2	69/F	Glioblastoma*	Nodular	Yes	5 mo
3	54/M	Malignant astrocytoma*	Nodular	Yes	3 wk
4	51/M	Primitive neuroepithelial tumor*	Nodular	Yes	8 mo
5	69/F	Oligodendroglioma*	Nodular	Yes	2 y
6	69/F	Metastases*	Nodular	Yes	3 wk
7	48/M	Glioblastoma*	Nodular	No	9 d
8	24/M	Glioblastoma*	Rim	No	7 d
9	62/M	Meningioma*	Rim	No	14 d
10	67/M	Meningioma*	Nodular	No	13 d
11	62/F	Pineal cyst	Rim	No	. . .
12	10/M	Intraventricular hemorrhage	Rim	No	. . .
13	54/M	Septic infarction	Rim	No	. . .
14	54/M	Septic infarction	Rim	No	. . .
15	54/M	Septic infarction	Rim	No	. . .
16	43/F	Arteriovenous malformation with hematoma	Rim	No	. . .

* Region of interest was the surgical site within this lesion.

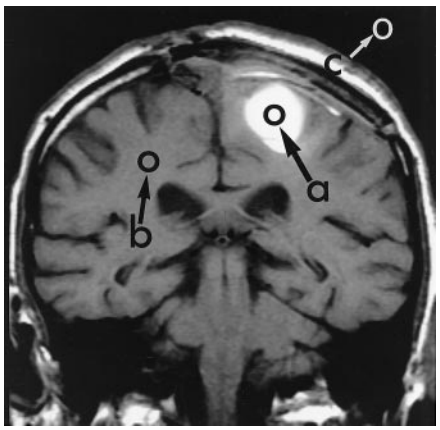

Fig 1. Locations of region-of-interest (ROI) measurements in the lesion (*a*), contralateral white matter (*b*), and background (*c*). (Actual ROIs used were smaller than shown.)

for precontrast and postcontrast images. Fat-saturation techniques were not used for any study.

Corresponding noncontrast and contrast-enhanced images were transferred to an independent workstation. Digital subtraction was performed with the use of standard software. The subtracted images were reregistered by using translation or rotation to obtain the optimal subtraction. ROI measurements were obtained at an identical location within the enhancing lesion on each set of images. ROI measurements were also obtained from background (air) and from white matter in the contralateral cerebral hemisphere (Fig 1). A circular ROI of 0.03 cm^2 was used for all measurements. The patterns of contrast enhancement were assessed visually on enhanced and subtracted images.

In cases 1 to 6 (all cases in which reverse enhancement was seen), the area from which ROI measurements were taken was a site of biopsy or partial resection of a malignant glial tumor that was surrounded by residual tumor and was obvious at surgery and imaging. Follow-up studies showed increasing tumor in all these patients; two of whom have since died. In cases 4, 5, and 6, repeat surgery was performed for enlarging residual tumor. The other two patients with malignant tumor (that did not show reverse enhancement) are still being followed up. Patient 7 had subtotal resection of a glioblastoma, which recurred 9 months later (currently, he has an enlarging recurrent tumor subsequent to repeat surgery). Patient 8 underwent 70% resection of a glioblastoma, which was stable at the 2-year follow-up. Two patients with postoperative meningiomas (cases 9 and 10) were included in our study. In one (case 9), gross total removal was done before scanning and no recurrence was seen on repeat MR studies 21 months later. The other patient (case 10) had subtotal resection and has stable residual disease.

The remaining six studies (in four patients) all showed nonneoplastic hematomas. Follow-up MR imaging has shown complete resolution in all cases. In case 16, an arteriovenous malformation and hematoma were surgically removed.

Results

All 16 studies were successfully subtracted. No images were corrected for rotational misregistration and no studies were rejected because of uncorrectable misregistration.

Subtracted images revealed rimlike or nodular marginal enhancement of all lesions (Table 1). A significant decrease in signal intensity was observed within the hemorrhagic central component in six cases (Tables 2 and 3 and Figs 2 and 3). No significant change in signal was seen

TABLE 2: Lesions showing reverse enhancement

Case	Diagnosis	Change (SD) in Signal from Precontrast to Postcontrast*			Intensity Ratio of Lesion to Brain on T2-Weighted Images
		Lesion	White Matter in Contralateral Hemisphere	Background Air	
1	Glioblastoma	−35.4 (5.2)	3.8 (6.1)	−0.6 (7.7)	3.1
2	Glioblastoma	−38.6 (3.7)	7.8 (10.5)	1.8 (7.8)	3.5
3	Malignant astrocytoma	−28.6 (3.6)	2.6 (7.5)	2.4 (11.2)	4.1
4	Primitive neuroepithelial tumor	−81.4 (9.8)	7.6 (9.3)	0.6 (5.1)	3.9
5	Oligodendroglioma	−29.0 (14.0)	1.4 (13.7)	0.6 (5.8)	3.8
6	Metastasis	−147.0 (8.3)	14.1 (7.8)	4.0 (9.1)	2.7
Average		−60.0 (7.4)	6.2 (9.1)	1.5 (7.8)	3.6

* *P* value for change in signal from lesion to brain was less than .01 for all cases.

TABLE 3: Lesions not showing reverse enhancement

Case	Diagnosis	Change (SD) in Signal from Precontrast to Postcontrast*			Intensity Ratio of Lesion to Brain on T2-Weighted Images
		Lesion	White Matter in Contralateral Hemisphere	Background Air	
7	Glioblastoma	10.0 (16.0)	8.1 (9.5)	2.2 (6.5)	2.9
8	Glioblastoma	4.8 (9.2)	1.7 (6.9)	0.9 (8.7)	3.3
9	Meningioma	−4.0 (12.0)	−0.8 (3.3)	0.6 (5.3)	3.5
10	Meningioma	0.0 (8.9)	3.5 (6.0)	1.3 (6.7)	3.0
11	Pineal cyst	4.5 (8.5)	1.3 (8.2)	0.9 (4.0)	2.5
12	Intraventricular hemorrhage	2.3 (6.1)	2.1 (6.9)	1.1 (3.8)	4.1
13	Septic infarct	−1.3 (7.7)	4.8 (7.2)	0.4 (5.5)	2.6
14	Septic infarct	−2.1 (4.7)	3.7 (6.3)	1.9 (4.5)	3.3
15	Septic infarct	3.5 (5.1)	2.9 (9.0)	0.8 (7.6)	3.2
16	Arteriovenous malformation with hematoma	4.3 (9.8)	3.1 (6.7)	1.3 (6.3)	3.7

* *P* values for change in signal from lesion to brain range from .15 to .49.

in the central portion of the lesion in 10 cases (Fig 4). In all six of the latter cases this decrease in intensity was visually obvious on the subtracted image but was subtle or not apparent on the conventional postcontrast image (Figs 2 and 3). All the lesions that showed a decrease in signal intensity after contrast enhancement were hemorrhagic areas associated with incompletely resected malignant tumor.

In all cases of reverse enhancement, visual assessment of T2-weighted images revealed at least moderate T2 prolongation within the hemorrhagic lesion (Figs 2 and 3). ROIs on T2-weighted images were significantly greater than surrounding brain in all cases (Tables 2 and 3).

Discussion

The usefulness of contrast-enhanced MR images in the evaluation of intracranial disease has been well documented (1). Since methemoglobin and gadolinium each produce high signal intensity on T1-weighted images (6, 7), contrast enhancement can be obscured by presence of subacute hemorrhage in the ROI. Subtraction effectively removes the component of hyperintensity created by blood to allow a clear view of tissue-enhancement characteristics (3).

In six of our cases, an interesting enhancement pattern was noted. In each of these cases, markedly hyperintense hematomas in the ROI were seen on the unenhanced T1-weighted images. After subtraction, the ROI was noted to be significantly less intense than the surrounding subtracted brain parenchyma or background, indicating that less T1 shortening was present on the postcontrast image than on the precontrast image. This phenomenon was noted previously by Yousem et al (4) upon visual assess-

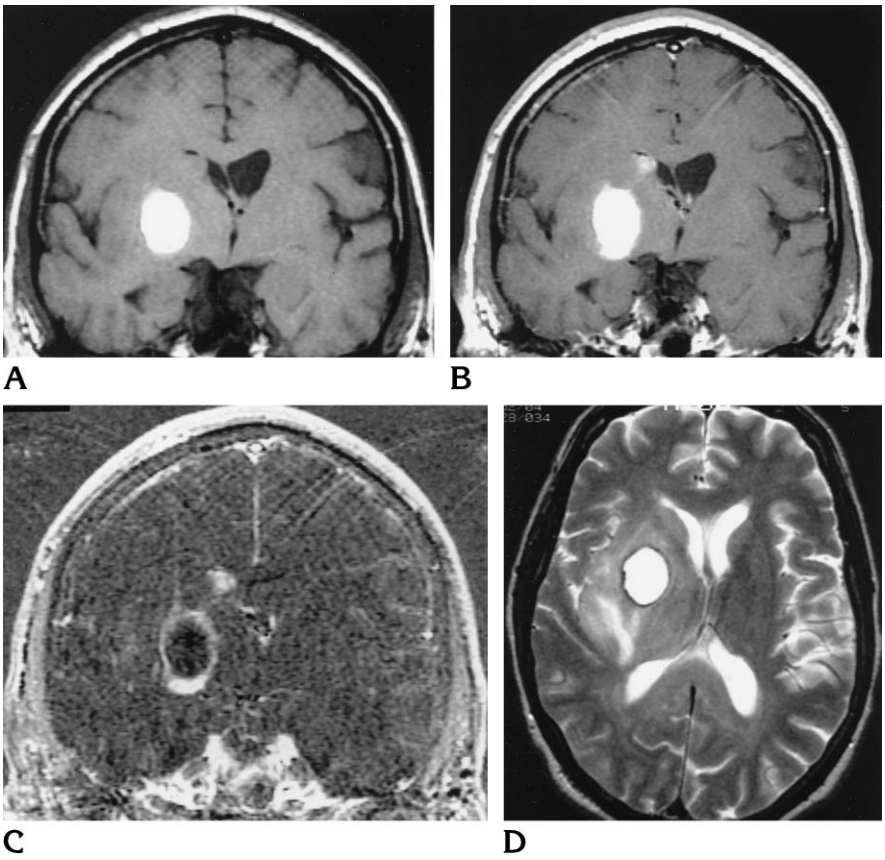

Fig 2. Reverse enhancement in a malignant astrocytoma deep in the right hemisphere is shown on precontrast (*A*) and postcontrast (*B*) T1-weighted coronal images (550/19/1 [repetition time/echo time/excitations]); on a subtracted image (*C*); and on a fast spin-echo T2-weighted axial image (3400/102/1) (*D*). Rimlike and nodular enhancement around the hematoma is evident in *B* but is best appreciated on the subtracted image, *C*, as is the decrease in signal within the hyperintense central portion of the lesion. An enhancing subependymal nodule adjacent to the body of the right lateral ventricle is well seen on postcontrast and subtracted images. The hematoma is markedly hyperintense on the T2-weighted image.

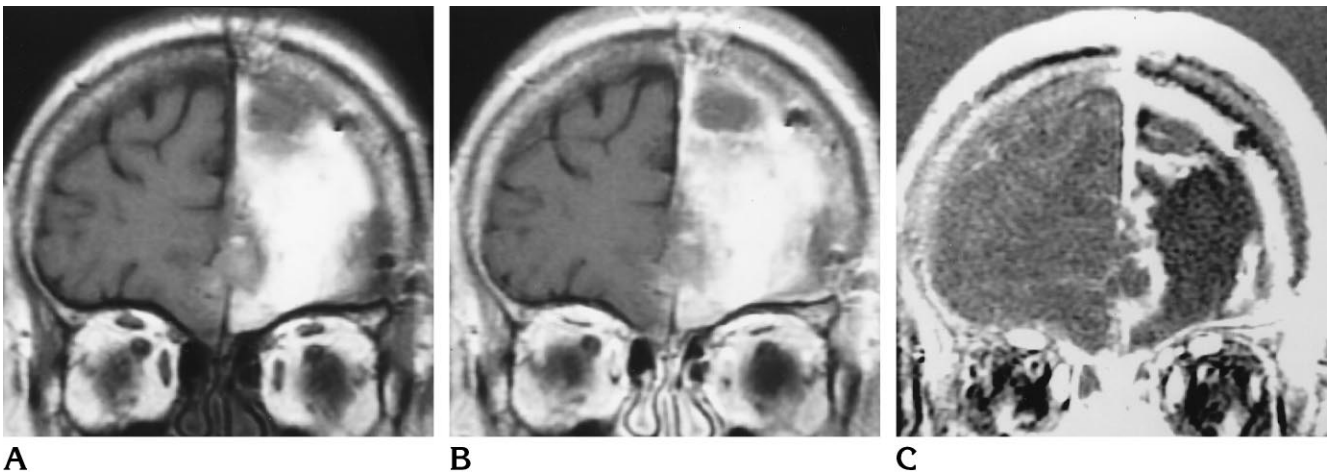

Fig 3. Reverse enhancement in a right frontal oligodendroglioma is seen on precontrast (*A*) and postcontrast (*B*) T1-weighted images (550/19/1) and on a subtracted image (*C*). The irregular nodular enhancement along the margins of the surgical bed and the central decrease in signal intensity are best appreciated on the subtracted image.

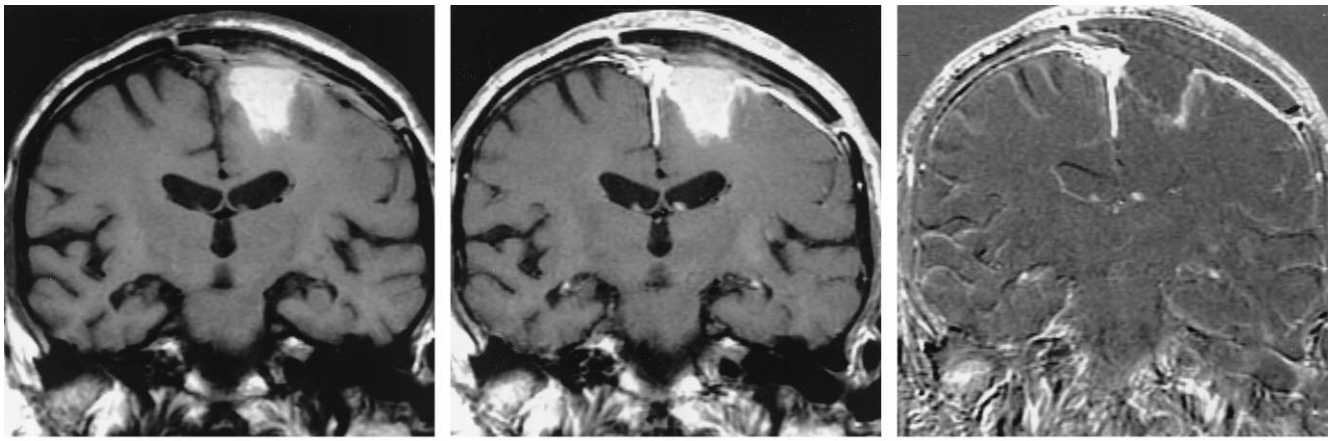

Fig 4. Lack of reverse enhancement in a left frontoparietal meningioma resection site is seen on precontrast (*A*) and postcontrast (*B*) T1-weighted image (550/19/1) and on a subtracted image (*C*). There is no appreciable decrease in signal intensity within the surgical bed on the subtracted image.

ment of seven cases. As precontrast and postcontrast imaging and photographic parameters were not kept constant in most of their cases, they speculated that the apparent decrease in intensity on postcontrast images may have represented "a perceptual artifact" or may have been associated with changes in repetition time, echo time, and gain values. However, ROI measurements were obtained in three of their cases in which these parameters were kept constant and confirmed a true decrease in signal, which they attributed to T2 shortening. A commentary on their article (5) suggested that the finding was most likely artifactual, as the authors themselves suspected, and that slight differences in patient positioning or site selection for ROI measurements may have contributed to the effect. Slight, visually imperceptible enhancement of normal brain surrounding the lesion, with a relative decrease in signal of the nonenhancing lesion, was also postulated. All these factors were eliminated in our study by the use of digital subtraction techniques and ROI measurements.

With any dipolar interaction, both T1 and T2 shortening may occur (4). Wang et al (2) describe an alteration in signal intensity seen on T1-weighted images obtained with increasing concentrations of gadolinium. The T1-shortening effect of gadolinium up to the peak enhancement level can be reasonably approximated by a straight line (2) (Fig 5). With higher concentrations of gadolinium, signal intensity actually starts to decline, owing to T2-shortening effects. The net change in signal intensity

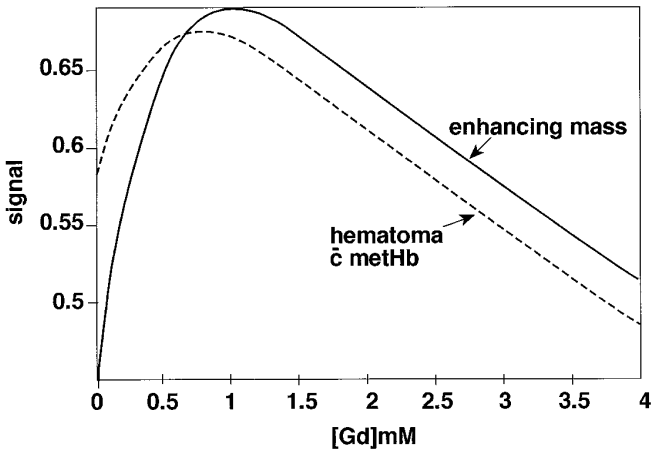

Fig 5. Comparison of intensity curve of gadolinium alone (*solid line*) versus estimated intensity curve of gadolinium plus methemoglobin (*dashed line*). In the presence of a second paramagnetic substance such as methemoglobin, the peak effect of gadolinium on signal intensity occurs at a slightly lower concentration, and T2 shortening effects occur earlier (after Wang et al [2]).

caused by increasing concentrations of methemoglobin follows a similar curve (7).

The addition of methemoglobin causes the hyperintensity resulting from T1 shortening to saturate at a lower concentration of gadolinium so that the signal reduction due to the T2-shortening effect of gadolinium becomes apparent at a lower concentration. T2-shortening effects are minimal with pure methemoglobin. In practice, subacute hematomas contain some T2-shortening substances, such as deoxyhemoglobin, even when the predominant effect on T2 signal intensity is due to extracellular methemoglobin.

The combination of two strong paramagnetic agents (methemoglobin and gadolinium) thus appears to cause the same effect as increasing the gadolinium concentration despite the minimal T2-shortening effects of methemoglobin. This resulted in a relative decrease in signal intensity on postcontrast images in six of our 16 cases. This shift to the left of the gadolinium concentration curve is illustrated in Figure 5.

It appears that visible T2 shortening prior to contrast injection is not a prerequisite for reverse enhancement. We did not obtain contrast-enhanced T2-weighted images, but all lesions were hyperintense on noncontrast T2-weighted images in the area in which this phenomenon occurred (Table 2). Future investigations of this effect should include precontrast and postcontrast digital subtraction T2-weighted images to confirm the contribution of T2 shortening.

Although reverse enhancement seems to be a relatively frequent phenomenon, it was often detectable only on the subtracted images, and its clinical significance is uncertain. However, it is possible that the combined effect of subacute hemorrhage and gadolinium may not permit optimal enhancement.

The only hemorrhagic lesions in this series that showed an alteration in signal intensity were malignant neoplasms. Only two malignant lesions did not show reverse enhancement, and in one of these a gross total resection had been performed 1 week before the scan. Nonneoplastic hematomas are thought to enhance only along their margins (8); with hemorrhagic tumor, contrast material may be delivered into the hematoma's fluid (4).

All the lesions showing reverse enhancement had been operated on, and this may have contributed to some difference in contrast delivery into the hematoma's fluid, owing to surgical interruption of the blood-brain barrier. Also, it is of interest that in the previous description of this phenomenon (4), four of the seven cases were pituitary adenomas, two were craniopharyngiomas, and only one was malignant (metastatic melanoma). Surgery certainly does not always cause reverse enhancement to occur; cases 7 through 10 were postoperative hematomas that did not show this effect.

In conclusion, postcontrast digital subtraction MR images may allow detection of a decrease in signal intensity within lesions containing methemoglobin, owing to high concentrations of two paramagnetic agents (gadolinium and methemoglobin), resulting in T2 shortening effects that overpower the effects of T1 shortening.

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