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NEURORADIOLOGY
CASE REPORT

Gadolinium leakage into subarachnoid space and cystic metastases

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ABSTRACT
Subarachnoid space (SAS) and cystic metastatic lesions of brain parenchyma appear hypointense on fluid-attenuated inversion-recovery (FLAIR) and T1-weighted magnetic resonance imaging (MRI) unless there is a hemorrhage or elevated protein content. Otherwise, delayed enhancement and accumulation of contrast media in SAS or cyst of metastases should be considered. We present hyperintense SAS and cystic brain metastases of lung cancer on FLAIR and T1-weighted MRI, respectively, in a patient who had been previously given contrast media for imaging of spinal metastases and had mildly impaired renal functions, and discuss the relevant literature.

Gadolinium (Gd) enhanced magnetic resonance imaging (MRI) is routinely performed for diagnosis and monitoring of various central nervous system diseases. On noncontrast T1-weighted imaging, most lesions are hypointense in the absence of blood products and diverse paramagnetic substances, fat or elevated protein content. Blood-brain barrier (BBB) damage and the related leakage of contrast media into the extracellular space from the vascular system result in abnormal enhancement following intravenous administration of Gd-based paramagnetic contrast materials. Therefore, numerous lesions of infectious, inflammatory, demyelinating, and malignant diseases are enhanced after contrast medium administration in the brain parenchyma (1). Gd accumulation within the cystic fluid of metastases causing a potential diagnostic misunderstanding has not been reported in the literature, to our knowledge.

On normal fluid-attenuated inversion-recovery (FLAIR) imaging, the inversion-recovery pulse nulls the signal from subarachnoid space (SAS), and it is hypointense unless there is accompanying blood, tumor, inflammation or infection, as well as vascular engorgement. These conditions include subarachnoid hemorrhage, meningitis, meningeal carcinomatosis, leptomeningeal metastases, subacute infarct, subdural hematoma, adjacent neoplasms, dural venous thrombosis, and status epilepticus (2, 3). Rarely, oxygen supplementation during MRI and previous Gd-based contrast media administration may result in hyperintense SAS. Gd accumulation in SAS may occur in patients with or without renal insufficiency, and in conditions with or without BBB damage (2–5). Herein, we present a case with Gd leakage into SAS and cystic fluid of metastases with a brief review of the literature.

Case report

A 48-year-old male with a metastatic lung cancer (squamous cell carcinoma) was admitted to our hospital with complaints of lower back pain and lower limb weakness for 20 days. He had received his last chemotherapy and radiotherapy treatment five months prior. On admission, neurological examination revealed lower limb paresis and paresthesia at T11–L1 dermatomes, and the patient reported urine and fecal incontinence. In laboratory tests, blood urea concentration was 23.98 mg/dL (normal range, 6–20 mg/dL), blood creatinine concentration was 1.39 mg/dL (normal range, 0.7–1.2 mg/dL), and glomerular filtration rate (GFR) was 54.31 mL/min/1.73 m^2 (estimated Modification of Diet in Renal Disease Formula GFR, <60 mL/min/1.73 m^2). Contrast enhanced whole spine MRI was performed using 0.01 mmol/kg gadopentetate dimeglumine for a suspected diagnosis of vertebral metastases and/or pathological fracture between T11 and L1 levels.

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MRI studies were performed on a 1.5 Tesla MR scanner (Symphony, Tim Systems, Siemens Medical Systems, Erlangen, Germany). Spine MRI demonstrated multiple bone metastases that were hypointense on precontrast T1-weighted imaging (Fig. 1a) and enhanced on postcontrast images throughout the spine. There were also enhancing pial nodular metastases adjacent to the spinal cord and at the cauda equina on postcontrast T1-weighted imaging. Marked edema of the spinal cord was observed between C7 and T4 levels without a remarkable intramedullary enhancement. At the time of spinal imaging, because extensive spinal intradural extramedullary metastases and enhancing metastases in the cerebellum were detected (Fig. 1a), additional postcontrast T1-weighted imaging of the brain was also obtained. It revealed leptomeningeal carcinomatosis and cystic metastases in the right cerebral and left cerebellar hemispheres with a peripheral enhancement and hypointense cystic fluid (Fig. 1b).

The patient was admitted to the medical oncology clinic with these findings. Approximately 24 hours after the first MRI, his physician, who was unaware of the postcontrast T1-weighted imaging of the brain obtained during the spine imaging session, requested a new brain contrast-enhanced MRI. . At this second MRI, SAS was hypointense but the cystic metastatic lesions were hyperintense on precontrast T1-weighted imaging (Fig. 1c). Additionally, SAS was diffusely hyperintense (Fig. 2a) and cystic metastases were bright on FLAIR imaging. Following intravenous administration of same contrast media with the previous exam, leptomeningeal carcinomatosis and widespread parenchymal micronodular metastases were also observed. Together, the findings from both imaging sessions suggested leakage of Gd from the vascular system into the central cystic fluid of parenchymal metastases and SAS. Two additional separate MRI, including T1-weighted imaging, FLAIR, and gradient echo (GRE) images, were performed to follow Gd clearance from cystic fluid of parenchymal metastases and SAS, and to rule out hemorrhage

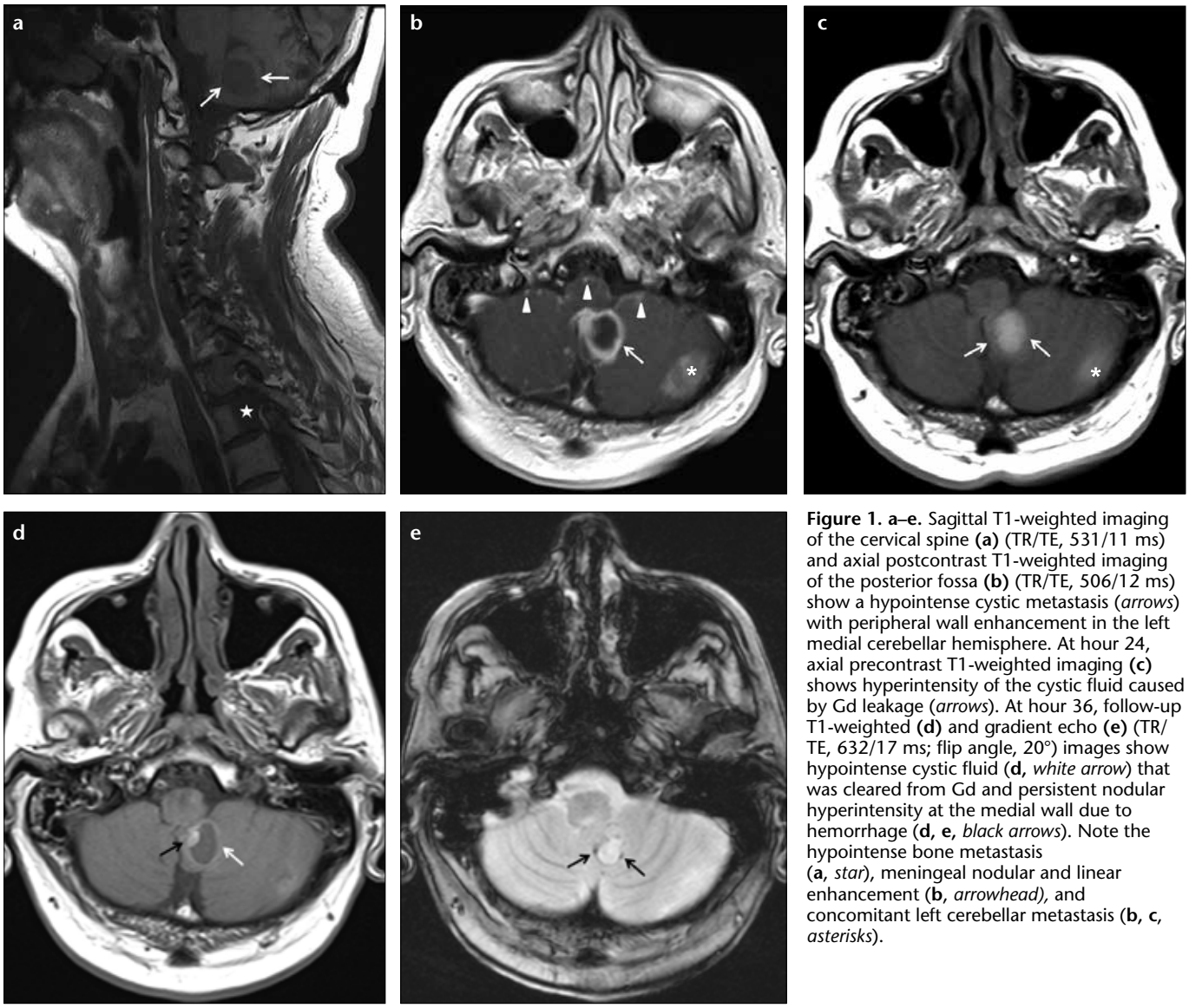

Figure 1. a–e. Sagittal T1-weighted imaging of the cervical spine **(a)** (TR/TE, 531/11 ms) and axial postcontrast T1-weighted imaging of the posterior fossa **(b)** (TR/TE, 506/12 ms) show a hypointense cystic metastasis (*arrows*) with peripheral wall enhancement in the left medial cerebellar hemisphere. At hour 24, axial precontrast T1-weighted imaging **(c)** shows hyperintensity of the cystic fluid caused by Gd leakage (*arrows*). At hour 36, follow-up T1-weighted **(d)** and gradient echo **(e)** (TR/TE, 632/17 ms; flip angle, 20°) images show hypointense cystic fluid (**d,** *white arrow*) that was cleared from Gd and persistent nodular hyperintensity at the medial wall due to hemorrhage (**d, e,** *black arrows*). Note the hypointense bone metastasis (**a**, *star*), meningeal nodular and linear enhancement (**b**, *arrowhead),* and concomitant left cerebellar metastasis (**b, c**, *asterisks*).

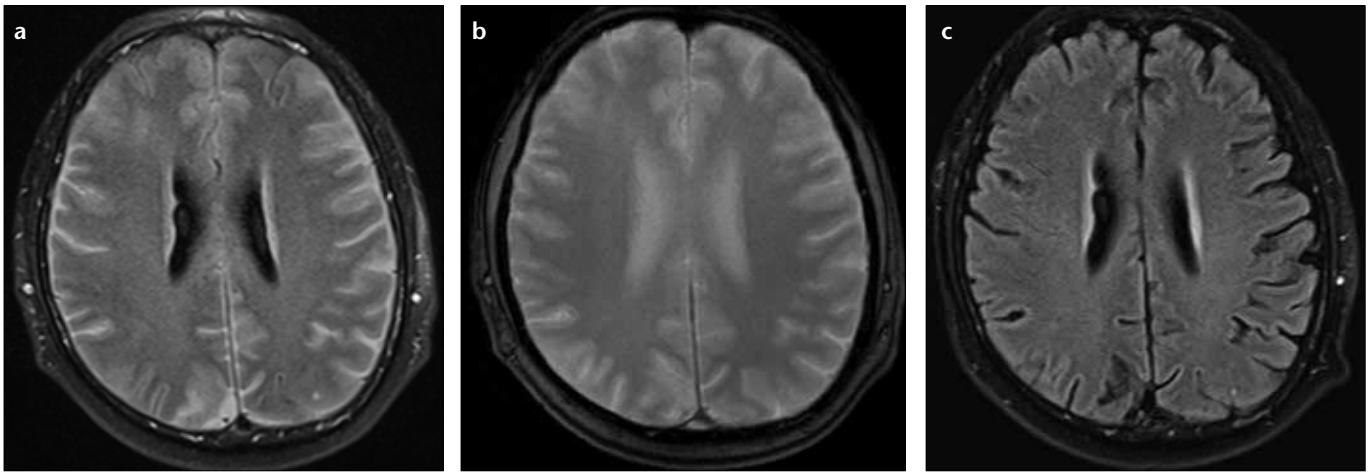

Figure 2. a–c. Axial FLAIR (TR/TE/TI, 8000/127/2183 ms) image at hour 24 **(a)** shows diffuse SAS hyperintensity due to Gd leakage. On the gradient echo image **(b)**, there is no evidence of hemorrhage. At hour 160, the follow-up FLAIR image **(c)** shows hypointense SAS with total clearance from Gd.

that might have also caused T1 shortening. The scans were performed at approximately 36 and 160 hours after administration of the contrast material. At 36 hours, cystic fluids of the parenchymal metastases were hypointense with continued enhancement at the periphery of the cyst on T1-weighted imaging (Fig. 1d) that may in part be due to hemorrhage observed on GRE imaging (Fig. 1e); SAS and cyst fluid, however, were still hyperintense on FLAIR imaging (not shown). On GRE imaging, SAS had no evidence of susceptibility (Fig. 2b). After 160 hours, SAS and cyst fluid were cleared of Gd on FLAIR images (Fig. 2c), but subtle T1 hyperintensity at the periphery of the cyst remained on T1-weighted imaging images.

The total dose of Gd given to the patient in the two scanning sessions was 30 mL (gadopentetate dimeglumine, 0.01 mmol/kg). During the hospital stay, renal function parameters of the patient were mildly impaired.

Discussion

Increased signal intensity in the SAS has been described in numerous pathologic changes of the meninges and brain tissue on FLAIR imaging, including subarachnoid hemorrhage, meningitis, meningeal carcinomatosis, leptomeningeal metastases, subacute infarct, subdural hematoma, adjacent neoplasms, dural venous thrombosis, and status epilepticus (2, 3). Additionally, supplemental oxygen during MRI and previous contrast media administration can also cause artifactual SAS hyperintensity (1, 4–6). According to Braga et al. (7), supplemental oxygen at 100% is a main cause of artifactual SAS hyperintensity on FLAIR imaging, regardless of the anesthetic drug used. This artifact does not develop when 50% oxygen is administered. Another cause for artifactual SAS hyperintensity is previous contrast media administration. In a large series of 33 patients, Bozzao et al. (8) demonstrated hyperintense SAS on FLAIR imaging due to Gd leakage in 2–24 hours following Gd administration in pathologic conditions with BBB disruption and neovascularization.

Although BBB disruption and neovascularization result in leakage of contrast media into the extracellular space from vascular system, there is no evidence from a histopathologic study showing that damaged pial vessels could allow leakage of Gd into the SAS. The exact mechanism of leptomeningeal and SAS enhancement remains unclear (1, 8). Notably, Morris and Miller (3) showed that presence of abnormalities known to disrupt the BBB and renal insufficiency are not mandatory for SAS hyperintensity on FLAIR caused by previous Gd administration. Their findings also suggested that Gd chelates might move across an osmotic gradient at the circumventricular organs with elevated plasma concentrations where there is no BBB, as in normal dura mater. An *in vitro* and animal model study by Mamourian et al. (9) with healthy dogs also showed that intravenously administered Gd could cross into the SAS in sufficient concentrations to alter the appearance of the SAS on FLAIR. They emphasized that SAS concentrations of Gd were proportional to the administered Gd dose, and that a dose three times higher than standard amounts (0.03 mmol/kg) was essential to produce detectable changes (9). Therefore, signal changes related to leakage of Gd into SAS require sufficient Gd concentration in the plasma and/or BBB disruption or neovascularization.

Not only is the total dose administered to the patient important in affecting the detection of Gd in the SAS and persistence of the hyperintensity on images, but also the persistence of Gd in plasma caused by renal functional impairment plays a role (10). Gd chelates are cleared from plasma via glomerular filtration, with a normal plasma half-life of 1.6 hours. In patients with renal insufficiency, the plasma half-life of Gd chelates may be prolonged up to 30 hours (11, 12). Hence, either renal insufficiency or an overdose administered to patients may be responsible for hyperintense SAS on FLAIR imaging.

In our patient, resolution of cystic fluid hyperintensity on T1-weighted images occurred at 36 hours, and both cystic fluid and SAS hyperintensity on FLAIR images was observed at 160 hours. In the literature, resolution of the hyperintensity on FLAIR or T1-weighted images, which developed following administration of gadopentetate dimeglumine and gadodiamide (5, 8, 9) ranged

between 48 hours to two weeks (3, 8-10). Although Bozzao et al. (8) stated that resorption time of Gd from SAS is 48 hours on FLAIR, no other study has investigated the exact resolution time of hyperintensity in varying conditions, including total dose or renal function degree. In the current patient, BBB disruption and abnormal plasma clearance due to mild renal functional impairment might have resulted in accumulation of Gd in cystic metastases, and SAS on T1-weighted and FLAIR images. Two administrations of Gd (15 cc each, for a total of 30 cc) within approximately 30 hours also might have prolonged the clearance of the Gd from the plasma and resulted in continued hyperintensity up to the 160 hours on FLAIR images.

In our patient, SAS hyperintensity on FLAIR could not be attributed to subarachnoid hemorrhage, as evidenced from GRE. However, the cystic metastasis located in the left medial cerebellar hemisphere had micronodular and peripheral susceptibility due to blood, and this may explain the lack of apparent signal alteration in the lesion wall on T1-weighted images from 36 to 160 hours. Still, the cystic fluid did not show hemorrhage on GRE, supporting our Gd-leakage hypothesis.

We also observed hyperintense cystic metastases on T1-weighted images caused by previous Gd administration. Breast cancer, adenocarcinoma of lung cancer, thymic squamous cell carcinoma metastases can be cystic/necrotic (13). Abnormally proliferating vessels of high-grade tumors have intercellular gaps and discontinuous basement membrane, causing both intravascular (flow related) and interstitial (permeability related) enhancement (1). Bozzao et al. (8) showed FLAIR hyperintensity of cystic cavities in a necrotic brain mass and a surgical cavity due to Gd leakage. Given that FLAIR is much more sensitive to changes in Gd concentration (9), we further demonstrated this finding on T1-weighted imaging.

In conclusion, radiologists should be aware of delayed or persistent Gd enhancement that can occur in cysts of the metastases (and possibly of other necrotic tumors), and SAS on T1-weighted and FLAIR imaging. In such situations, radiologists should check history of previous Gd administration in the patients, especially in those without renal impairment.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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