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Utility of Susceptibility Weighted Imaging (SWI) in the Detection of Brain Hemorrhagic Metastases from Breast Cancer and Melanoma

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Abstract

Purpose—SWI has significantly increased our sensitivity in detecting hemorrhagic brain lesions. We sought to explore the prevalence of intra-tumoral hemorrhage as detected by SWI in brain metastases from melanoma and breast cancer.

Methods—Lesions with a size of 0.1 cm^3 were categorized as micro-metastases while larger lesions were categorized as macro-metastases. SWI findings on locations corresponding to enhancing lesions were categorized as either positive or negative based on presence/absence of signal dropout. The percentage of SWI positivity was then estimated as a function of lesion size. Two-tailed Fisher's exact test was performed to examine differences in the contingency tables.

Results—MRI studies from 73 patients with 1,173 brain metastases which enhanced on post-contrast T1-weighted imaging (T1WI) were selected for analysis. Of these lesions, 952 had SWI data available, and 342 out of 952 were micro-metastases. Only 10 of the 342 micro-metastases and 410 of the 610 macro-metastases were SWI positive (67.2%, p-value of < 0.0001). When examined by tumor type, 76.9% (melanoma) versus 55.6% (breast cancer) were SWI positive (p-

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Ethical Standards and Patient Consent: We declare that all human and animal studies have been approved by our institutional ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

Authors' contribution to the Manuscript: AM Franceschi: project development, data collection, manuscript writing
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value < 0.0001), regardless of tumor size. All melanoma lesions (8/8) and only 1 out of 15 breast cancer lesions larger than 1.5 cm^3 were SWI positive.

Conclusion—Using combined SWI and contrast-enhanced high-resolution T1 imaging we found that presence of intra-tumoral brain hemorrhage is uncommon in micro-metastases but common in metastases > 0.1 cm^3 from breast cancer or melanoma. Large metastases commonly harbored hemorrhage and this occurred more frequently in patients with melanoma than with breast cancer.

Keywords

brain; micro-hemorrhage; susceptibility weighted imaging; melanoma; breast cancer

Introduction

Spontaneous intracerebral hemorrhage is a potentially devastating disease that can be the end result of various conditions, including malignancies. Although acute hemorrhage can be the presenting sign of a primary brain malignancy, distinct metastatic brain tumors may have a higher propensity (e.g. thyroid, choriocarcinoma, melanoma, and renal cell carcinoma) or a higher prevalence (e.g. breast and lung cancer) of intratumoral hemorrhage than primary brain tumors. [1] Apart from the obvious potentially catastrophic consequences of symptomatic intra-tumoral brain hemorrhage, little is known about the biology and prognostic implications of occult intracranial hemorrhage. It has been recently shown that histopathologic detection of hemorrhage in routine hematoxylin and eosin-stained sections from patients who have undergone craniotomy for melanoma and breast cancer brain metastases can be an adverse prognostic factor. [2, 3] Given the obvious limitations of craniotomy-based research to generalize findings, non-invasive (i.e. imaging) detection of intra-tumoral hemorrhage across various cancer types, in particular the association between clinico-pathologic and radiographic features (e.g. contrast enhancement, number and size of metastases), holds promise to refine prognosis and improve treatment decisions.

Development of the susceptibility weighted imaging (SWI) sequence has significantly increased our sensitivity to noninvasively detect the venous vasculature, blood products, and changes in iron content of brain lesions. [4] In the case of brain tumors, SWI sequence complements, or even supersedes, tumor detection and other characteristics, such as boundaries, architecture of tumor vasculature, and presence of blood products identified by conventional T1-weighted contrast-enhanced imaging. [5] Due to the distinct intralesional susceptibility signal(s) within brain lesions, SWI in conjunction with conventional MRI has been previously used in glioma grading as well as in the differential diagnosis of enhancing brain lesions. [6-8] With respect to solid tumors, SWI has been recently used to understand the primary tumor characteristics of patients with clear-cell type renal cell [9-10], hepatocellular [11], and prostate carcinomas. [12] A single study investigated the sensitivity of detecting hemorrhage in brain metastases from patients with lung cancer compared to conventional contrast enhanced MRI sequences. [13] In this study, we sought to explore the prevalence of intra-tumoral hemorrhage as detected by SWI in patients with brain metastases from melanoma and breast cancer, and to correlate it with tumor size.

Materials and Methods

Patient Selection

This retrospective study was approved by our Institutional Review Board (IRB). Patients were identified from the Outpatient Melanoma and Breast Cancer Clinics database, where they were receiving clinical care and follow up. Enrolled subjects had histologically confirmed melanoma or breast cancer, and brain MRI imaging studies at the time of the initial diagnosis of brain metastases. All contrast-enhancing brain lesions were presumed to be metastatic foci. Patients with a history of prior brain surgery or radiation were excluded due to the potential for local treatment-induce hemorrhage that would yield signal abnormalities on SWI. Only MRI studies that were performed at the time of diagnosis of brain metastases were included in the analysis. Additionally, MRI studies were reviewed for image quality, and studies with motion and other artifacts were excluded from the analysis.

Image Acquisition

All patients were scanned at 3T using a standard 12-channel phase array body-matrix coil. Contrast-enhanced images were obtained immediately following intravenous administration of 0.1 ml/kg gadobenate dimeglumine (MultiHance®, Bracco Imaging, Princeton, NJ) with a T1-weighted fat-suppressed spoiled gradient echo sequence as follows: Axial gradient echo (GRE) T1-weighted imaging [TR/TE/TI (9.7/4.0/300) field of view, 240-mm; voxel size, 1.3× 1.3 × 1.2-mm; slice thickness, 1.2-mm; flip angle, 15. SWI were obtained before the administration of contrast as follows: (TR/TE (28/20), field of view, 240-mm; voxel size, 1 × 1 × 1.5-mm; matrix size, 192×256; reconstructed slice thickness, 6 mm (obtained from four 1.5 mm thick slices), flip angle, 20).

Image Analysis

All contrast-enhancing brain lesions by conventional MRI sequences were identified for each patient in a picture archiving and communication system (PACS) workstation and were considered brain metastases based on consensus opinion of the medical oncologist and neuroradiologist. Readers were blinded to the cancer type (i.e. melanoma versus breast cancer). For assessment of individual tumor volumes, the maximal and orthogonal diameters of each lesion were measured in the axial plane. The depth of each lesion was then measured by counting the number of slices where each lesion was visible on the T1 sequence. An ellipsoid volume, V, for each lesion was then calculated through the following equation:

$$(\mathrm{V}=4/3\pi * \mathrm{a} * \mathrm{b} * \mathrm{c})\,.$$

Where a, b, c, is the maximal diameter, orthogonal diameter and depth of each lesion, respectively. Micro-metastases were defined as contrast-enhancing lesions ≤ 0.1 cm^3 in size. Each of the brain metastases was classified as hemorrhagic or not by comparison with the best matching SWI slice.

Statistical Analysis

A two-tailed Fisher exact test was performed to examine differences in the contingency tables (breast versus melanoma brain metastases, hemorrhage versus non-hemorrhage).

Results

Overall 1,173 contrast-enhancing brain lesions were identified in 73 patients. Of these lesions, 952 had SWI sequence data available for analysis. 38 of the subjects had breast cancer (467 analyzed lesions) and 35 had melanoma (485 analyzed lesions). Only 10 of 342 micro-metastases had SWI abnormalities, while 410 of 610 (67.2%) larger lesions were SWI positive and thus hemorrhagic (p-value < 0.0001). When examined by primary tumor type, 76.9% (melanoma) versus 55.6% (breast cancer) were SWI positive (p-value < 0.0001). All melanoma lesions (8/8) larger than 1.5 cm^3 were SWI positive, while 14 of 15 similar breast cancer lesions were SWI negative. (Fig. 1)

Discussion

The development of hemorrhage within brain metastases has been attributed to the presence of abnormal, leaky vessels within the tumor. Histological studies have identified common features associated with hemorrhage, including tumor necrosis, vessel-wall hyalinization, necrosis of the vessel walls and vessel rupture. [14] The expression of vascular endothelial growth factor (VEGF) and matrix-metalloproteinases (MMP -2 and -9) has also being associated with the presence of hemorrhage. Rapid growth of a tumor induces hypoxia which in turn stimulates VEGF production. The MMP family of proteinases plays the important role of degrading the extra-cellular membrane and microvascular integrity, and in turn, likely further weakens the blood vessel walls. Various explanations for the presence of hemorrhage have been proposed ranging from direct invasion to venous thrombosis, while choriocarcinoma metastases are considered a special case due to the direct invasion of vessels by the tumor. [15]

Our study investigated the incidence of intratumoral brain hemorrhages as detected by SWI in untreated brain metastases from cohorts of patients (≥ 35 patients each) with metastatic melanoma and breast cancer. Identification of intra-tumoral hemorrhage in metastatic brain tumors is clinically important for treatment decisions. The increased sensitivity of SWI sequence is due to the use of the phase signal altered by the presence of deoxyhemoglobin and hemosiderin deposited within metastases. Previous histopathologic analysis suggests that intra-tumoral hemorrhage may be prognostic in melanoma but not in breast brain metastases and that non-invasive identification of hemorrhage may also have disease-specific prognostic implications. [2, 3] The higher incidence of hemorrhage seen in melanoma as opposed to breast brain metastases seen in our patients is in agreement with a previous study that predominantly focused on quantification of intra-tumoral susceptibility signals in SWI sequences obtained in patients who underwent brain MRI for metastatic brain tumors from melanoma, breast cancer, and lung cancer as well as with previous analysis of hemorrhage and other histopathologic factors in representative tumor sections from large cohorts of specimens that were collected as part of craniotomies for brain metastases from melanoma or breast cancer. [16]

Our second aim was to correlate tumor size with presence of hemorrhage on SWI. It has been suggested that, despite the unique biology that may account for the increased propensity of melanoma to bleed as compared with breast brain metastases, other factors such as tumor size may play a role. [17] Although in our patients incidence of hemorrhage was higher in larger size tumors (>1.5 cm^3) and was significantly lower to absent in micro-metastases irrespective of tumor type, we again identified that for a given tumor size, melanomas metastatic to the brain had a higher incidence of hemorrhage compared to breast brain metastases.

Overall, the relatively low prevalence of SWI detectable hemorrhage in micro-metastases would limit its utility in detecting micro-metastases when used independently. However, in patients with impaired renal function or contrast agent allergies, SWI does offer the potential to detect metastases without the use of contrast. Others have proposed its use in attempting to distinguish between primary and metastatic brain tumors, and understanding the prevalence of SWI abnormalities in metastases would assist in understanding its predictive value. [18] The difference in hemorrhage prevalence also points to different biological mechanisms for brain invasion by the metastases and emphases the need for a better understanding of the underlying pathophysiology. [2]

Caveats in our study include the lack of histopathologic proof that all enhancing lesions were indeed metastases. Furthermore, we did not compared the results of SWI with other sequences, such as pre-contrast T1 and gradient echo images, as it is known that SWI is superior to these sequences in detecting hemorrhage. Also, we did not seek prognostic or survival information or correlated our findings with genetics/biological status of the lesions.

Conclusions

Using SWI and contrast enhanced high resolution T1 imaging we found that presence of hemorrhage is uncommon in micro-metastases but common in larger metastases regardless of primary source, melanoma vs. breast cancer. Larger metastases from these two primaries commonly harbored hemorrhage and this occurred more often with melanoma than with primary breast cancer.

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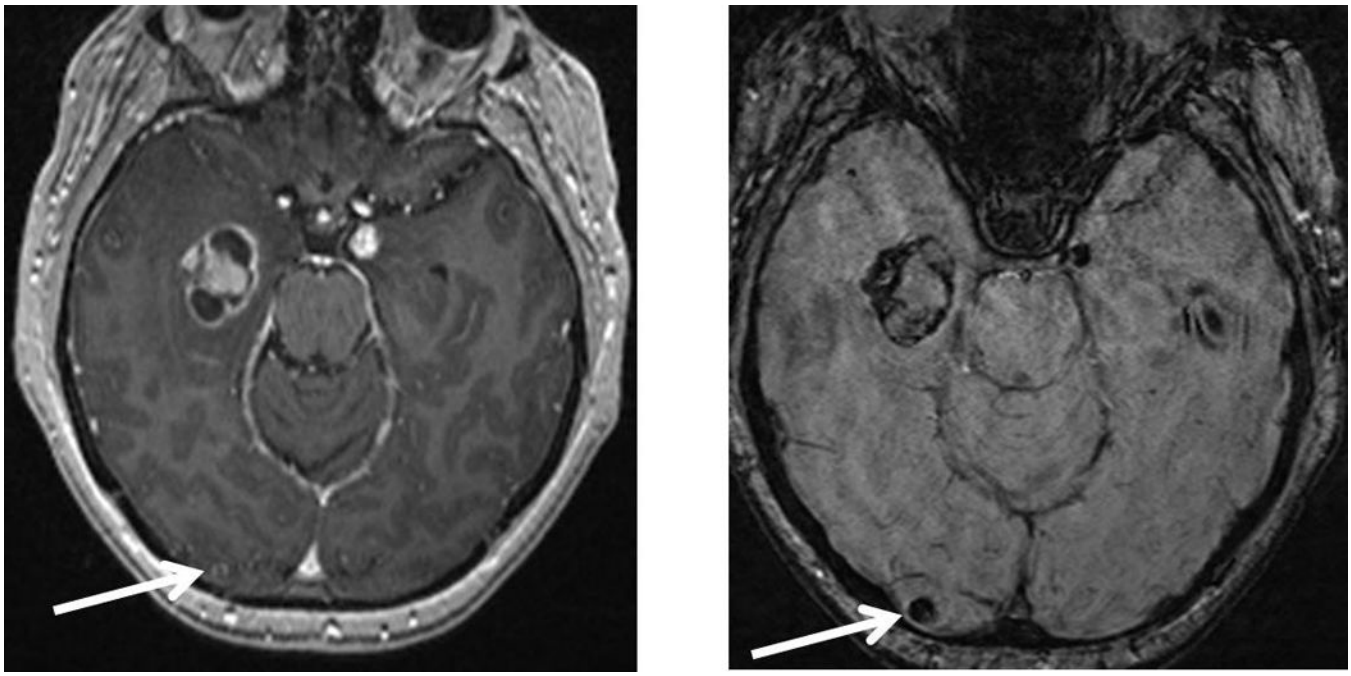

Figure 1.

(a) Post contrast T1 image shows multiple enhancing lesions in patient with known metastatic melanoma. **(b)** Corresponding SWI demonstrates low signal intensity in the larger right mesial temporal lesion, the small left amygdala lesion and in the smaller right occipital lesion (arrow) which is difficult to appreciate on A due to overlying artifacts from flow in the posterior sagittal sinus.