Anatomical relationships between medullary veins and three types of deep-seated malignant brain tumors as detected by susceptibility-weighted imaging

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1. INTRODUCTION

Metastases, high-grade gliomas, and primary central nervous system lymphomas (PCNSLs) are adult brain malignancies commonly encountered in neuroradiologic diagnostic settings. Accurate preoperative diagnoses of these malignancies are crucial so that their distinct managements and prognoses are properly applied.\textsuperscript{1–3} The differential diagnosis of the three brain malignancies is challenging because their neuroimaging presentation are highly variable and overlapping with each other. For example, each of them can occur as single or multiple masses, appear as circumscribed or well-enhanced lesions in either cerebral hemisphere, and can be accompanied by necrosis or hemorrhage. This is particularly true when a metastatic tumor is solitary and/or located in the deep structure of the brain rather than exhibiting the more commonly presented multiple and superficial presentation.

These deep-seated malignant tumors are similar in conventional magnetic resonance (MR) imaging sequences such as fluid attenuation inversion recovery imaging and T1-weighted (T1W) contrast enhancement patterns, which reflect only the degree of blood-brain barrier breakdown.\textsuperscript{4,5} Advanced MR imaging sequences, including diffusion-weighted images, provide information about apparent diffusion coefficient maps, where low values are observed in brain tumors because of their high cellular density,\textsuperscript{6} a common factor in all three of these tumor types. The metabolic information revealed by MR spectroscopy benefits diagnosis. However, variations in study quality, patient population, and study design have caused heterogeneity between individual studies, limiting the application.\textsuperscript{7}

Susceptibility-weighted imaging (SWI) is a new MR sequence that uses gradient-recalled echo phase images to demonstrate the smallest susceptibility variations in the corresponding magnitude images.\textsuperscript{8–10} This sequence has been used to differentiate PCNSLs from high-grade gliomas by the number of susceptibility-based signals or intratumoral susceptibility signals. The
presence of intratumoral susceptibility signals can be used to
differentiate between glioblastomas and PCNSLs with high sen-
sitivity (91.2%) and specificity (93.3%). Also, SWI is highly
sensitive for detecting intravascular venous deoxygenated blood
even when the venous vasculature is smaller than one voxel
because paramagnetic deoxyhemoglobin is used as an intrin-
sic contrast agent. Therefore, small medullary veins in deep
brain structures can easily be detected, an outcome that has not
been achieved with conventional MR imaging. Since these small
medullary veins are distal part of the deep venous system, their
territory will be used to define whether a tumor is deep-seated
and to observe the anatomical relationships between tumors and
adjacent small medullary veins in this study.

Histologically, these three malignant tumor types have dis-
tinct growth patterns that can affect how each is associated with
medullary veins. High-grade glioma is infiltrative, and PCNSL
is characterized by a cluster of malignant lymphocytic cells sur-
rounding the pre-existing vessels. Vessels can be entrapped
within either of these two tumor types. In contrast, a metastatic
brain tumor has a well-defined border and pushes brain paren-
chyma and adjacent pre-existing vessels away. Based on
this differing characteristic, we hypothesized that the anatomi-
cal relationships between tumors and adjacent small medullary
veins would differ in these three common types of malignant
brain tumors, and that SWI, which is adept at detecting small
medullary veins, could provide crucial information that would
allow differentiation.

2. METHODS

2.1. Patients

This study was approved by the Joint Institutional Review
Board of Taipei Medical University (approval no. N2016030381).
Informed consent was waived because the study was a retro-
spective review.

The database maintained by the Pathology Department at
our institution showed that 72 patients had pathologically con-
firmed PCNSLs, high-grade gliomas, or metastatic brain tumors
between May 2009 and March 2015. Records were reviewed,
and patients were excluded if motion artifacts were marked or
if only postoperation or postbiopsy SWI images were available.

Patients were included if complete MR images, including SWI
sequences, were available and if their tumors were deep-seated
in the territory of small medullary veins, which was defined as
the epicenter of at least one tumor located medial to the ipsi-
lateral imaginary line drawn connecting the endpoints of each
medullary veins of one side (Fig. 1; see Fig. 2C for the example
of a deep-seated tumor).

Based on the above-mentioned criteria, a total of 54 patients,
including 11 PCNSLs, 9 high-grade gliomas, and 34 metastases,
were recruited for analysis. Among these cases, there were 11
PCNSLs, 5 high-grade gliomas, and 13 metastases in the medul-
lar vein territory. Seven metastases in the cerebellum were not
enrolled.

2.2. MR imaging protocol

All MR imaging studies were performed at our institution using
a 1.5-T scanner (Magnetom Avanto; Siemens Medical Solutions,
Erlangen, Germany) with a standard 12-channel head coil. After
the routine T1W and T2-weighted fluid attenuation inversion
recovery sequence, SWI and contrast-enhanced T1 sequences
were performed. To assess the morphology and margin of the
brain tumor, contrast-enhanced T1 was performed with a TR/
TE of 552/17 ms, a flip angle of 90º, a field of view of 23 cm, a
matrix of 224 × 256, and a slice thickness of 5 mm.

For the transverse three-dimensional SWI sequences, the set-
tings were as follows: TR/TE, 49/40 ms; flip angle, 15º; slice
thickness, 2 mm with 60 sections per slab; matrix, 224 × 256; 64
slices; and acceleration factor, 2 for the integrated parallel acqui-
sition technique. Minimal intensity projection (minIP) images
were reconstructed with an effective minIP thickness of 16 mm.
The sequence and all image processing were automated using the
Siemens MR scanner platform based on the concepts by Haacke et
al. The phase, magnitude, minIP, and SWI images were uploaded
and made available on a picture archiving and communication
system (IMPAX 6.4; AGFA Healthcare, Mortsel, Belgium). The
total scan time for all protocols was less than 30 minutes.

2.3. Image interpretation

All MR images were reviewed together by two neuroradiologists
(S.-H.Y.: 6.5 years of neuroradiologic experience and C-Y.C.: 21
years of neuroradiologic experience) who were blinded to

Fig. 1 The selection process used to find patients with malignant brain tumors. MRI = magnetic resonance imaging; PCNSL = primary central nervous system lymphoma; SWI = susceptibility-weighted imaging.
the pathological diagnoses. Tumoral extent and margin were defined by enhancing a part of the axial contrast-enhanced T1W images. The definition of small medullary veins are veins that merge from the subcortical area, directly cross the white matter, and drained into the subependymal veins.15 These small medullary veins are not easily identifiable in conventional MR sequences but can be seen in SWI or minIP images as linear and contiguous dark signal intensities perpendicular to the lateral ventricular wall, tapering in the subcortical regions. The anatomical relationships between small medullary veins and tumors in this study were interpreted by correlating contrast-enhanced T1W images with SWI slice by slice until the two neuroradiologists reached consensus for each patient. Different patterns of anatomical relationships were categorized based on the presence of a medullary vein blockage (MVB).

MVB-positive was defined as a small medullary vein terminating at the margin of the tumor (Fig. 2), while MVB-negative was defined when a small medullary vein contiguously penetrated through the tumor along the vessel course without terminating at the margin (Figs. 3 and 4) or the intratumoral SWI signal was unable to be differentiated from blockage or penetration (Fig. 5). When multiple qualified lesions were present and any one exhibited an MVB, the patient was classified as MVB-positive.

2.4. Statistical analysis
The association between the presence of MVB and tumor pathology was analyzed. Descriptive statistics (e.g., mean ± SD or frequency with percentage) were calculated for all variables using IBM SPSS for Windows, Version 19.0 (Released 2010; IBM Corp., Armonk, NY.)

3. RESULTS
Table 1 shows patient demographics for those who met our inclusion criteria. Age range was 41 years to 93 years, and 15 of the 29 were female. Table 2 tabulates the number of patients who were MVB-positive or -negative and the malignant brain tumor diagnoses.

For deep-seated metastatic brain tumors, majority (76.9%, 10 of 13) were MVB-positive while none of them presented with small medullary vein penetration. The three MVB-negative cases were classified so because extensive intratumoral dark signal in SWI made it impossible to discriminate if a small medullary vein was blocked outside or penetrated into the tumor. The sensitivity and specificity of the MVB sign for diagnosing deep-seated metastatic brain tumors were 76.9% and 100%, respectively, and diagnostic accuracy was 89.7%.

Neither of the two nonmetastatic tumor types exhibited MVBs. In all patients with PCNSL tumors and high-grade gliomas, there was at least one small medullary vein penetrating through tumors. The anatomical association between the small medullary veins and the tumors failed to differentiate between these two tumor types.

4. DISCUSSION
We identified a unique pattern of anatomical relationships between small medullary veins and tumors in SWI. The MVB...
sign was common and exclusively present in deep-seated metastatic brain tumors. This is in accordance with the distinct growth patterns of metastatic tumors found in pathology. To the best of our knowledge, this is the first SWI study to apply the anatomical relationships between small medullary veins and tumors to differentiate deep-seated malignant brain tumors in adults.

It is well known that the borders between a metastatic tumor and the parenchyma are usually distinct without infiltration to the brain parenchyma. Hence, most pre-existing vessels in brain parenchyma are likely to remain outside the tumor by either being destroyed or pushed away. This hypothesis was supported by our finding that MVB was detected by SWI in 10 of 13 patients in this study. Those patients who were classified as MVB-negative had extensive dark signal inside the tumor that prevented the interpreter from differentiating if a small medullary vein was blocked outside or penetrated into the tumor (Fig. 5).

Interestingly, in two of the patients with metastatic tumors, there were also larger deep veins (anterior terminal vein and superior thalamostriate vein, respectively) mildly displaced by tumors. These deep veins are subependymal veins and run tangentially to tumoral margins. Both of them were close to relatively large metastatic tumors (the diameter was 5.8 cm for one in the left frontal lobe and 4.7 cm for another in the right peri-trigonal region, while the mean diameter of the metastatic tumors was 4.0 cm). The mass effect and perifocal edema normally presented in large metastases might have displaced these large veins before destructing or blocking them.

Metastatic tumors of the brain are typically located in the corticomedullary junctions and usually do not require biopsy unless the tumor origin is unknown. In this study, biopsy-proven metastases represented difficult differential diagnoses. Atypical location for a metastatic brain tumor usually presents a challenging preoperation diagnosis, and the presence of the MVB
sign in the medullary vein territory can improve the diagnostic accuracy for deep-seated metastatic brain tumors.

Metastatic brain tumors are managed differently from those that are PCNSLs and high-grade gliomas. For example, a primary lesion will be sought out before biopsy if the cancer history is unknown. In this study, we found that MVB was seen exclusively in SWI for deep-seated metastatic brain tumors with a relative high accuracy of 89.7%. This finding assures that application of the MVB sign in clinical practice would likely be beneficial.

Histologically, a PCNSL typically demonstrates patchy, poorly demarcated, angiocentric proliferation of tumor cells that invade the parenchyma or subarachnoid space through the perivascular cuffs.22 Lymphoma cells tend to infiltrate pre-existing parenchymal vessels rather than destroy them, and the tumor is usually deeply seated. Similarly, high-grade gliomas are among the most vascularized malignant tumors and show an infiltrative growth pattern. The malignant cells proliferate, and this is followed by endothelium proliferation and abundant angiogenesis.23 Due to the growth patterns, these two tumor types tend to engulf small medullary veins within the tumor mass. Therefore, it is not surprising that in this study the two types of tumor presented no MVB, and commonly demonstrated continuous penetration of small medullary veins through the tumor. The high-grade gliomas may also show small medullary vein passing through the nonenhanced tumoral areas (Fig. 4) because mixed grades of high-grade gliomas were not unusual, and the microscopic infiltrative margin could not easily be delineated in postcontrast images.

Small medullary vein penetration in SWI could not be used to differentiate PCNSLs from high-grade gliomas given that this study included a small number of cases. However, it could well be a typical sign for PCNSL; it was detected in all 11 PCNSLs in this study, and similar results can be found in other locations throughout the human body. Examples include the “sandwich sign” of lymphomas involving the mesentry,24 the CT “angio-gram sign” of primary pulmonary lymphomas,25 and the “small-vessel sign” of lymphomas involving peripheral lymph nodes.26,27 Without the penetration sign, PCNSLs might need to be evaluated carefully. Further studies would be helpful for differentiating PCNSLs from other malignant brain tumors.

This study has limitations. This study recruited only pathology confirmed brain tumors; therefore, the population size is small. Only 29 tumors met our inclusion criteria, limiting the level of detailed analysis. For example, the numbers of GBM cases in the current study were too small (five patients) for statistical analysis. The relatively low occurrence of our research target—deep brain tumors that required a biopsy—explained partly why the case numbers are small. Nonetheless, those types of tumors are diagnostic challenges and our finding provides a neuroimaging feature that has not been described before. Additionally, this retrospective study lacked a one-to-one radiology-pathology correlation to demonstrate the image findings in the tissue sample. However, the entire picture of the relationship between medullary veins and the tumor, as detected by SWI, could be difficult to confirm pathologically through a regular small-sized tissue biopsy. Finally, SWI resolution in our protocol limited the comprehensive observation of the three-dimensional anatomical relationships between the tumors and medullary veins even after using reformatted coronal and sagittal views. This could be resolved in the future using faster and higher-resolution image acquisition, available from a 3-Tesla MR imaging machine.

In conclusion, the unique MVB sign delineating the anatomical relationship between medullary veins and deep-seated brain tumors provides an additional diagnostic clue about the brain metastasis in the medullary vein territory. This sign could be useful for preoperatively differentiating deep-seated metastatic tumors from the other two common primary malignant brain tumors.

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