Differentiation of tubercular infection and metastasis presenting as ring enhancing lesion by diffusion and perfusion magnetic resonance imaging

Différenciation entre infection tuberculeuse et métastase d’une lésion rehaussée en périphérie par IRM de diffusion et de perfusion


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KEYWORDS
Brain; Tuberculosis; Metastasis; Perfusion; Diffusion; Ring enhancing

Summary
Background and purpose. — As both tuberculoma and metastasis can manifest as solitary or multiple ring-enhancing intra-axial lesions that are difficult to differentiate by conventional magnetic resonance imaging (MRI), we hypothesized that the use of diffusion and perfusion MRI would make differentiation of these pathologies possible.
Materials and methods. — Diffusion and T2*-weighted dynamic contrast-enhanced perfusion MRI scans from 11 patients with histologically proven tuberculoma or metastasis were retrospectively reviewed by two radiologists who were blinded to the pathology. All patients had a ring-enhancing lesion on conventional MRI. Apparent diffusion coefficient (ADC) values and regional cerebral blood volume (rCBV) were calculated from the walls of the lesions.
Results. — Lesions showed different perfusion characteristics depending on whether they were due to tuberculosis or metastasis. The mean rCBV ratio between the lesion periphery and normal white matter was inferior to one for tubercular lesions and greater than five for metastases. However, ADC values were similar.
Conclusion. — Measuring rCBV obtained by T2*-weighted dynamic contrast-enhanced perfusion MRI can help in differentiating intracranial tuberculatous mass lesions and metastases.
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Introduction

Ring-enhancing lesions in the brain always raise questions among radiologists and, given the many possible differential diagnoses, it may sometimes be difficult to reach a diagnosis.
Figure 1  A, B. T2-weighted (T2W) and post-contrast T1-weighted (T1W) images show a ring-enhancing lesion in the posterior fossa with central hypo-intense areas on T2W imaging; C. Susceptibility-weighted imaging (minimum intensity projection) shows no obvious blooming suggestive of hemorrhage; D. rCBV color map shows marked hypoperfusion in the mass lesion with no evidence of high perfusion areas in the peripheral enhancing portions (white arrow); E, F. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) images show no evidence of restricted diffusion within the mass lesion. The histopathology of the lesion is suggestive of tuberculoma.

Figure 2  A, B. T2W and post-contrast T1W images show a ring-enhancing lesion with a thick wall in the left parafalcine area and a hyperintense center surrounded by an iso-intense periphery on T2W imaging; C. Susceptibility-weighted imaging (minimum intensity projection) shows no exaggerated blooming suggestive of hemorrhage; D. rCBV color map shows markedly increased perfusion at the margin of the lesion (white arrow); E, F. DWI and ADC images show facilitated diffusion in the center (corresponding to necrosis) and mild restricted diffusion in the wall of the mass. The histopathology of the lesion is suggestive of metastasis.

with conventional imaging. Tuberculosis and metastasis are among the most common differential diagnoses whenever ring-enhancing lesions are encountered, especially in cases with multiple lesions. In clinical practice, it is essential to differentiate between these two conditions because their management and prognoses are totally different. Although in a few cases, a biopsy may be performed for confirmation of the diagnosis, a number of patients are empirically started on antituberculosis therapy [1] solely on the basis of imaging findings. Indeed, this is a common practice in many developing countries because of the high incidence of intracranial tuberculosis. However, the response to antituberculosis therapy may take several months and, during this period, both the patient and the treating physician are presuming that the patient has tuberculosis. Such a belief, however, may be fatal for the patient who harbors metastases.

This means that it is essential, especially when the diagnosis is based on imaging, to have imaging techniques that can differentiate these entities. Advanced magnetic resonance imaging (MRI) techniques such as diffusion, perfusion and MR spectroscopy (MRS) may be used for this. However, as lipid peaks are described in both these lesions, MRS may not be helpful [2]. Furthermore, the spectra may not be representative within small lesions and may be of poor quality if there is hemorrhage or calcification within the lesion. For this reason, we used only diffusion and perfusion imaging parameters in this study. Also, we restricted our study to a small group of patients in whom the diagnosis was histopathologically proven. This was because, as already mentioned, the majority of these patients have been started on antituberculosis treatment. Although the number of patients included was small, this was the first study attempting to differentiate between tuberculosis and metastasis presenting as ring-enhancing lesions through the use of advanced MRI techniques.

Materials and methods

One of the present authors (C.S.) retrospectively carried out a search in our departmental imaging database of the past three years and three months. A total of 13 patients with histopathologically proven tuberculosis and 15 patients with histopathologically proven metastatic lesions involving the brain were selected for inclusion in our study. Of these 28 patients, only 11 had ring-enhancing lesions on conventional MRI. However, diffusion and perfusion sequences had been performed in all these patients, as is routinely required by our departmental imaging protocol for all intra-axial mass lesions. The patients with metastases comprised four women and three men, aged 30—60 years (mean age: 42.57 years), while those with tuberculosis included three men and one woman, aged 7—36 years (mean age: 20 years). Inclusion criteria for our study were:

- ring-enhancing lesions on post-contrast T1-weighted (T1W) images;
- available perfusion and diffusion data;
- histopathological confirmation of the diagnosis;
- no history of antituberculosis chemotherapy or steroids before imaging.

MRI examinations were performed using a superconducting, whole-body, SQ-engine 1.5-T MAGNETOM Avanto system (Siemens, Erlangen, Germany) with a 12-channel head coil. After scout-view MRI, the examination protocol consisted of pre-contrast conventional MRI, followed by diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI) and, finally, post-contrast T1W images. Conventional MR images were obtained with T1W (fast spin-echo [FSE], 442/15) and turbo T2W (turbo spin-echo [TSE], 3510/110) sequences (both with a 382 × 512 matrix, 5-mm slice thickness and 1 average) as well as T2*-weighted (susceptibility-weighted imaging [SWI], 48/40/20°) sequences. DWI was acquired using single-shot echo-planar imaging (EPI) sequences at multiple levels and in three orthogonal directions (20 slices of 5-mm thickness, repetition time [TR] 3500 ms, echo time [TE] 105 ms, field of view 230 × 230, matrix size 192 × 192, b value of 0 and 1000s/mm²).

For susceptibility-based PWI, the transitory signal loss during the bolus passage was detected with a T2*-weighted gradient EPI sequence (TR 1800 ms, TE 43 ms, 20 slices with 5-mm slice thickness and 1.5-mm interslice gap, matrix 128 × 128 and 1 average). A total of 50 dynamic scans with a time resolution of 1.0s/image were performed after intravenous bolus injection of 15 mL of gadolinium (Gd)-DTPA (Omniscan, GE Healthcare) at a flow rate of 5 mL s⁻¹, and a 20-mL saline flush.

The apparent diffusion coefficient (ADC) and perfusion data were analyzed by two radiologists (S.J., C.K.) who were blinded to the histopathology results, and who were provided with only the axial contrast-enhanced T1W, diffusion and perfusion imaging data. The ADC maps and values were calculated at a dedicated workstation (Leonardo Workstation; Siemens Medical Systems, Erlangen, Germany). Lesional and perilesional edema were defined on the contrast-enhanced T1W images and the region of interest (ROI) was positioned over the area of the lesions on the ADC maps. The ROI for ADC measurement was positioned over those portions of the lesions that had the lowest signal intensity on ADC maps.

Raw PWI scans were transferred to the Leonardo Workstation for post-processing. With the aid of specific software, the rCBV was calculated on the basis of the indicator dilution method and displayed as color-spectrum images. For calculation of the perfusion indices, three circular ROI measurements were drawn over the regions of maximum abnormality, according to the color-coded rCBV maps. Regions that were clearly hemorrhagic — visualized as exaggerated blooming on SWI (minimum intensity projection) — were avoided. ROI with maximum values were used for the analyses. ROI analyses were also performed on the contralateral normal white matter. In addition, we measured the ratio of the maximum rCBV in the tumor relative to that in the contralateral normal white matter to compensate for variations on each examination.

For both the DWI and PWI study analyses, ADC and rCBV ratios were recorded by the two radiologists in consensus.

**Results**

Tubercular and ring-enhancing metastasis could be discriminated on the basis of perfusion imaging. All lesions showed areas of a relatively hypo-intense signal intensity on T2W images. Post-contrast-enhanced MRI revealed ring enhancement and/or solid enhancement with a central

| Table 1 Analyses of the apparent diffusion coefficient (ADC) and perfusion maps. |
|---------------------------------|---------------------|----------------|----------------|
| Patient                        | Number of lesions  | Lesion T2W signal intensity vs. cortex | ADC (10⁻³ mm² sec⁻¹) | rCBV ratio |
|--------------------------------|---------------------|----------------|----------------|
| Tuberculosis 1                 | Multiple            | Iso-intense with hypo-intense areas    | 129.87           | 1.38       |
| Tuberculosis 2                 | Multiple            | Iso-intense with hypo-intense areas    | 94.82            | 0.56       |
| Tuberculosis 3                 | Multiple            | Hypo-intense                               | 122.26           | 1.25       |
| Tuberculosis 4                 | Single              | Hypo-intense                               | 103.80           | 0.39       |
| Metastasis 1 (carcinoma; not otherwise specified) | Multiple | Peripheral iso-hypo-intense rim with central hyperintense area | 130.20 | 3.64 |
| Metastasis 2 (carcinoma, breast) | Single            | Heterogeneous signal intensity            | 107.06           | 4.27       |
| Metastasis 3 (carcinoma, breast) | Multiple            | Hypo-intense                               | 73.50            | 6.14       |
| Metastasis 4 (squamous cell carcinoma, bronchus or esophagus) | Single | Hypo-intense                               | 94.23            | 9.10       |
| Metastasis 5 (squamous cell carcinoma, bronchus) | Multiple | Hypo-intense                               | 93.52            | 5.65       |
| Metastasis 6 (adenocarcinoma, gut) | Multiple            | Iso-hypo-intense peripheral rim with central hyperintensity | 99.65 | 2.70 |
| Metastasis 7 (carcinoma, breast) | Single            | Hypo-intense                               | 108.50           | 3.90       |

T2W: T2-weighted; rCBV ratio: relative cerebral blood volume (ratio between brain lesion and normal white matter).

non-enhancing area. Diffusion and perfusion MRI findings are presented in Tables 1 and 2. Mean ADC values were $101.24 \times 10^{-3}$ mm$^2$ sec$^{-1}$ for metastases, and $112.68 \times 10^{-3}$ mm$^2$ sec$^{-1}$ for tuberculosis; ADC values for the two conditions were overlapping. However, all cases of tuberculosis showed lower rCBV ratios compared with metastasis cases. All cases showed reduced perfusion at the center of the lesion although, at the periphery, colored areas indicative of increased rCBV were seen in two cases of tuberculosis and all cases of metastasis. Nevertheless, the intensity was much greater in cases of metastatic lesions and was visibly evident on the color-coded maps (Figs. 1 and 2). The mean rCBV ratio between the lesion periphery and normal white matter was inferior to one for tubercular lesions and greater than five for metastasis cases, and was very low in the center and in the surrounding edematous areas.

**Discussion**

Differentiation of infective and non-infective lesions of the brain is of major clinical importance because of differences in their management and prognoses. Conventional MRI can help to distinguish infective and neoplastic ring-enhancing lesions [3]. However, such imaging findings are not always helpful, whereas advanced MRI techniques such as diffusion MRI, diffusion tensor imaging (DTI), perfusion MRI and MR spectroscopy may be useful in differentiating the two types of lesions [4–6].

Central-nervous-system tuberculosis remains a major problem in developing countries. Cerebral tuberculosis can manifest as a diffuse form such as basal exudative leptomeningitis, as a localized form such as focal tubercular lesions or as part of disseminated tuberculosis [7]. On imaging studies, focal tubercular lesions can be difficult to differentiate from other intracranial mass lesions and, in such cases, biopsy may be necessary to make the diagnosis [8]. However, focal tubercular lesions can have variable appearances on MRI [9,10]. Focal granulomatous lesions (tuberculomas) show variable signal intensity on T2W images and may appear as ring-enhancing lesions in post-contrast studies. Lesions with solid central caseation may appear hypo-intense on T2W images whereas lesions with central liquefactive necrosis may show T2 hyperintensity [11], and tubercular abscesses appear hyperintense on T2W images. Necrotic brain metastases are an important differential diagnosis of ring-enhancing brain lesions and may be difficult to differentiate from tuberculomas on conventional MRI as both may be seen as single or multiple ring-enhancing lesions. Adenocarcinoma metastases are also known to exhibit low signal intensity on T2W images [12,13]. This means that metastatic lesions may resemble solid caseating tubercular granulomas on conventional MRI.

On DWI, T2W hypo-intense tuberculous lesions show higher ADC values and look similar to minimally necrotic primary brain neoplasms [9]. Tuberculous abscesses may show restricted diffusion similar to that of pyogenic abscesses. Necrotic primary brain neoplasms show higher ADC values compared with tuberculous lesions [9,14]. However, metastatic lesions show variable signal intensity on DWI depending on their degree of differentiation and cellularity [13]. In the present study, the ADC values for metastases and focal tubercular lesions were overlapping and did not help to differentiate between the two entities.

However, a number of studies have proved the value of perfusion MRI in discriminating various cystic lesions of the brain [4–6,15]. These studies all showed differences between neoplastic and non-neoplastic lesions in terms of lower perfusion values in the infective lesions. Yet, none of these studies made any direct comparisons of the perfusion characteristics of tubercular and metastatic lesions. In most of these studies, the perfusion characteristics of glioma and pyogenic brain abscess were compared. However, in our clinical experience, differentiation of tuberculoma and metastases is more difficult because of their multiple and morphological similarities. Batra and Tripathi [16] studied the perfusion characteristics of parenchymal tubercular lesions and found variable rCBV in tubercular lesions. They concluded that perfusion values of tuberculosis overlap with those of other hypervascular neoplastic lesions of the brain.

Angiogenesis occurs in both neoplastic lesions and infective pathologies of the brain [17,18]. Vasoactive endothelial growth factor (VEGF), along with other cytokines, plays an important role in the angiogenesis and increased vascular permeability seen in both neoplastic and infective lesions [19–21]. VEGF expression, and the resulting pattern of angiogenesis and microvascular remodeling, are transient and mostly seen during the active phase in the course of a benign disease. In contrast, in cases of neoplastic conditions, angiogenesis is persistent, and has an influence on tumor proliferation and its spread as a result of continuous shedding of VEGF from tumor cells. This finding has been corroborated by dynamic contrast-enhanced studies of solitary pulmonary nodules where the slope of the initial contrast uptake was similar for both malignant and acute inflammatory conditions whereas, in cases of tuberculomas, the upslope was less steep, indicating relatively poor vascularity [22,23].

In the present study, we found differences in the perfusion characteristics between tuberculous and metastatic lesions. The mean rCBV ratio calculated in cases of tuberculous lesions was $0.90 \pm 0.49$ while that of metastases was $112.69 \pm 16.18$.
5.06 ± 2.13. The mean rCBV ratio for metastases was similar to that reported in the literature, although the rCBV ratio for tubercular lesions was lower than those reported by Batra and Tripathi [16] and Haris et al. [4]. The differences are possibly due to the different methodology as well as technique. Haris et al. used T1W dynamic contrast-enhanced MRI, which provides more accurate values of rCBV as the leak factor is taken into consideration. High permeability in abnormal regions leads to extravasation of contrast material into the interstitium, leading to significant underestimation of rCBV in T2*-weighted dynamic susceptibility-weighted perfusion MRI [24]. This difference in rCBV ratio between the two groups of patients adds power to the diagnostic confidence.

In the present preliminary descriptive study, its drawbacks were the small number of study cases and the lack of quantitative correlation for angiogenesis. As only histologically proven cases were included, the number of cases was reduced even further. However, there was clearly a large difference between the perfusion parameters of the two types of lesions. Nevertheless, a larger prospective study with statistical analysis is needed to ascertain whether or not the rCBV ratio can reliably discriminate between metastases and tuberculomas.

References