Tumefactive Multiple Sclerosis: a diagnostic dilemma. How useful is multimodal MRI?

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Learning objectives

Through the presented case series, the learning objectives are to:

- Recognise the difficulties associated with diagnosing tumefactive multiple sclerosis from clinical presentation and conventional imaging.
- Illustrate the role of multimodal MRI with a focus on spectroscopy, diffusion and perfusion imaging to increase diagnostic confidence.

Background

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system in which there is focal demyelination. It can either be of the relapsing-remitting or progressive clinical type. It is the commonest cause of progressive neurological disability in 20 to 40 year old adults in the developed world and has a significant social and economic impact [1-2]. The usual characteristic imaging findings are of multiple well-defined lesions without significant mass effect or oedema in the peri-ventricular white matter. Acute lesions typically cause blood-brain barrier breakdown which is associated with perivenous inflammation [3]. A small group of MS patients however present with lesions that mimic imaging appearances and symptoms of a neoplastic mass lesion, making it extremely difficult to differentiate between the two [4].

'Tumefactive MS' is the term given when clinical and imaging findings are indistinguishable from those of a neoplastic mass lesion. This is estimated to occur in about 1-2 out of every 1000 cases of MS [5]. Lesions will typically have ill-defined borders, mass effect, surrounding oedema, central necrosis, contrast enhancement and variable involvement of grey matter structures [6]. It is a rare presentation of the disease and due to diagnostic challenges, many centres will perform biopsy for diagnosis, however histopathology findings can be misleading and lead to unnecessary treatment [4]. There is evidence from case reports, that multimodal MRI can be used to aid the diagnosis of tumefactive MS, however this is not widely performed. In addition, current evidence is confusing and sometimes conflicting, leading to inaccurate interpretation. In this case series, we present three patients with features suggestive of a neoplastic mass lesion in which biopsy was avoided by careful interpretation of conventional and multimodal MRI revealing a diagnosis consistent with tumefactive MS.

Findings and procedure details
A retrospective review was performed on three patients between June 2013 and November 2014 at the Queen Elizabeth Hospital, Birmingham who had features suggestive of a neoplastic mass lesion. All the patients were female with an age range between 42 to 63 years. Biopsy was avoided by careful interpretation of multimodal MRI revealing a diagnosis consistent with tumefactive MS.

MRI was performed in all patients using a 3.0 T MR scanner with a 32 channel head coil. Sagittal and axial T1-weighted images, axial T2-weighted fast spin-echo (SE) images, and fluid-attenuated inversion recovery (FLAIR) images, with a field of view (FOV) of 25 to 35 cm, an image matrix of 256×128 or 256×256, and a section thickness of 5 mm with a 1 mm gap, were obtained for unenhanced sequences. Diffusion-weighted imaging (DWI) sequences were acquired in the axial plane using a single shot, SE planar imaging sequence with b-values of 0 and 1000 s/mm² in three orthogonal directions. Contrast-enhanced sagittal, coronal and axial T1-weighted SE-MRI images were obtained after the administration of gadolinium diethylenetriamine pentaacetic acid (0.1 mmol/kg body weight). Magnetic resonance spectroscopy (MRS) using the point resolved spectroscopy (PRESS) technique was carried out for single voxel and multi-voxel tumour evaluation. Both short echo time (TE 30 ms) and intermediate TE (135 ms) techniques were used to allow unambiguous detection of a greater number of metabolites including myo-inositol (mI), lipids and lactate, thus enhancing the diagnostic yield. Multi-voxel spectroscopy was carried out using 2D and 3D chemical shift imaging (CSI) (PRESS, TR 1700 ms, TE 30 or 135 ms) to investigate the spatial distribution of the metabolite profiles relative to the contrast-enhancing lesion and surrounding regions. The spatial resolution was 10 mm and 15 mm isotropic for the 2D and 3D chemical shift imaging (CSI) respectively.

All images were retrospectively reviewed by two experienced neuroradiologists. The images were specifically evaluated for lesion location, size, shape, margin, signal intensity, enhancement characteristics and presence of peri-lesional oedema. MRS, DWI and perfusion-weighted imaging (PWI) data was processed and analysed on a dedicated workstation.

Case 1

A previously fit and well 42 year old lady presented in February 2014 with slurred speech and right sided weakness. Over the previous month she had experienced episodes of dysarthria and right sided paraesthesia, however these resolved spontaneously. On examination she had dysarthria, expressive dysphasia, and a right sided hemiplegia (power 0/5 right upper limb (RUL) and 1/5 right lower limb (RLL)) with brisk reflexes. The patient’s MRI head scan revealed a large well defined T2 hyperintense lesion in the left periventricular and semiovale white matter measuring 3.8cm in diameter, with incomplete rim enhancement but without significant mass effect (Fig. 1 on page 5 A-B). The patient was commenced on methylprednisolone and symptoms improved slightly.
Infective and immunology screen returned unremarkable, however lumbar puncture revealed unmatched oligoclonal bands. Multi-disciplinary team meeting discussion recommendations were for possible biopsy of the lesion for a diagnosis, to ascertain whether it was lymphoma, multiple sclerosis or a primary tumour.

For further characterisation, MRS, DWI and PWI was performed (Fig. 1 on page 5 C-F). DWI and the apparent diffusion coefficient (ADC) map showed peripheral restricted diffusion and a central area of free diffusion within the lesion. PWI showed high relative cerebral blood volume (rCBV) values throughout the lesion. Multi-voxel CSI spectroscopy (TE 30 ms and 135 ms) revealed a high choline/creatine (Cho/Cr) ratio, near normal N-acetylaspartate/creatine (NAA/Cr) ratio, no presence of ml, presence of lactate at 1.3 ppm, and high glutamine and glutamate (2.3 ppm and 2.4 ppm respectively). The multimodal MRI findings were suggestive of acute tumefactive demyelination rather than a neoplastic cause.

The contralateral and normal appearing white matter also showed high choline, high glutamine and glutamate and the presence of lactate (Fig. 1 on page 5 G). These findings further supported the diagnosis of demyelination rather than a neoplastic lesion [7]. Consequently, biopsy was avoided and the patient was treated with a five day course of plasma exchange with some improvement in symptoms. Two weeks later a repeat MRI showed similar spectroscopic findings, but an increase in the lesion size. A further three days of plasma exchange was given and MRI showed features to suggest regression of the lesion six weeks from presentation. The patient was discharged with a tapering dose of prednisolone and seen two weeks later when power was almost 4/5 in the RUL and 5/5 in the RLL. Serial imaging showed gradual improvement and the eight month follow-up MRI showed regression of lesion (Fig. 2 on page 6 A-D).

**Case 2**

A 42 year old lady with a seven year history of relapsing-remitting multiple sclerosis presented to hospital in June 2013. She was on second line fingolimod treatment for the past few months due to ongoing relapses, before which she had taken interferon for three years. She was normally fully independent. The patient presented with a two day history of confusion, headache and difficulty speaking. Over the previous 24 hours she also had progressive right-sided weakness. On examination there was right sided hemiparesis and severe expressive/receptive dysphasia. MRI head scan revealed a large heterogenous space occupying mass lesion with a cystic component and septations (Fig. 3 on page 7 A-D) DWI and ADC images showed free diffusion centrally and a thin rim of restricted diffusion with non-contiguous rim enhancement. The differential diagnosis included aggressive primary glial neoplasm, intravascular lymphoma, progressive multifocal leukoencephalopathy and tumefactive MS. Cerebrospinal fluid showed inflammatory changes with a negative infective and cytopathology screen, and absence of oligoclonal bands. Vasculitic and autoantibody
screen was negative. Methylprednisolone was commenced and biopsy was considered to obtain a diagnosis.

The case was discussed at a multi-disciplinary team meeting and a decision was made for the patient to have MRS and PWI (Fig. 3 on page 7 E). 2D CSI showed a high Cho/Cr ratio, near normal NAA/Cr ratio, high glutamate and glutamine, low mI/Cr ratio, and the presence of lipid and lactate at 0.9 ppm and 1.3 ppm respectively. The metabolic profile from the adjacent peri-lesional area showed a similarly abnormal spectral pattern (Fig. 3 on page 7 F). PWI showed a relatively low rCBV except in the anterior-superior component. The enhancement pattern corresponding to perivenous inflammation and appearances remained atypical for a neoplastic lesion. The combined findings raised the possibility of tumefactive MS. High grade glioma and lymphoma were almost certainly ruled out in the context of clinical presentation, MRS, DWI and PWI findings.

Biopsy was not performed and a tapering dose of oral prednisolone was commenced, during which neurological symptoms improved. Follow-up imaging one month after presentation showed significant improvement in mass effect, midline shift and overall volume of the lesion. As a result of this, the patient was able to start second line disease modifying drug treatment with natalizumab and showed significant clinical improvement. An eight month follow-up MRI showed near normal imaging appearances and spectral pattern (Fig. 4 on page 8 A-E).

Case 3

A 63 year old woman presented initially in 2007 with headaches; MRI brain at the time revealed a posterior right frontal white matter lesion 2.9 cm in diameter suspicious of a possible low-grade tumour (Fig. 5 on page 9 A-B). It showed some central enhancement. Surveillance scans had been carried out since. Apart from a severe dizzy spell in March 2013, the patient remained asymptomatic and had no neurological deficit. A decision was made to further characterise the lesion using MRS, DWI and PWI in January 2014 (Fig. 5 on page 9 C-F). There was no restricted diffusion and a linear enhancement pattern was seen which was not nodular, likely to be perivenous. Single voxel spectroscopy (SVS) and 2D CSI showed a minimally raised Cho/Cr ratio, near normal NAA/Cr ratio, normal mI/Cr ratio, trace of lactate at 1.3 ppm and presence of glutamate and glutamine at 2.3-2.5 ppm. These features appeared to be consistent with a chronic demyelinating lesion rather than low or high grade glioma. In view of this, a decision to undergo biopsy was overturned and surveillance imaging was performed. Stable findings were seen on MRI ten months later (Fig. 6 on page 10 A-F).
**Fig. 1:** Case 1; a patient with tumefactive demyelination. (A) T2 FLAIR axial image shows a large well defined space occupying lesion in left central semiovale white matter. (B) Post-contrast T1-weighted image. (C-D) DWI and ADC map shows peripheral restricted diffusion. (E-F) Multi-voxel CSI spectroscopy revealed high Cho/Cr ratio, near normal NAA/Cr ratio, no presence of ml, presence of lactate at 1.3 ppm, and high glutamine and glutamate (2.3 ppm and 2.4 ppm respectively). (G) The contralateral and normal appearing white matter also shows high choline and high glutamine and glutamate. Arrows show locations chosen for MRS.
Fig. 2: Case 1; eight month follow-up MRI shows regression of the lesion. (A) T2 FLAIR axial image and (B) Post-contrast T1-weighted image shows a decrease in the size of the lesion. (C-D) DWI and ADC maps shows normalization of diffusion.
Fig. 3: Case 2; a patient with known MS presents with a mass lesion. (A) T2-weighted image shows a large space occupying lesion in left frontal lobe with peri-lesional oedema and mass effect. (B) Post-contrast T1-weighted image. (C-D) DWI and ADC images show a thin rim of restricted diffusion. (E-F) Multi-voxel spectroscopy shows a high Cho/Cr ratio, near normal NAA/Cr ratio, high glutamate and glutamine, low ml/Cr ratio, and the presence of lipid and lactate at 0.9 ppm and 1.3 ppm respectively. The metabolic profile from the adjacent peri-lesional area also showed a similarly abnormal spectral pattern. Arrows show locations chosen for MRS.
**Fig. 4:** Case 2; eight month follow-up scans. (A-D) There is near complete resolution of the mass lesion. (E) 2D CSI MRS shows improvement in the spectral pattern. There is a decrease in the Cho/Cr ratio, glutamate and glutamine as well as lipid and lactate. Arrow shows location chosen for MRS.

**Fig. 5:** Case 3. (A-D) T2-weighted image, post-contrast T1-weighted image, DWI and ADC images show a posterior right frontal white matter lesion. (E-G) Single voxel MRS with TE 30 ms shows a typical spectrum for demyelination. There is a slightly raised Cho/Cr ratio, near normal NAA/Cr ratio, normal mI/Cr ratio, trace of lactate at 1.3 ppm.
and presence of glutamate and glutamine at 2.3-2.5 ppm. 2D CSI with TE 30 ms shows similar findings. Single voxel MRS with TE 135 ms confirms lactate inversion at 1.3 ppm. Arrows show locations chosen for MRS.

**Fig. 6:** Case 3. (A-F) Ten month follow-up MRI shows stable radiological appearance with similar DWI, PWI and spectral findings. Arrows show locations chosen for MRS.
Conclusion

Tumefactive MS has been estimated to affect 0.1 to 0.2% of patients with MS [5]. There is some evidence from case reports that SVS can be used to aid in the diagnosis of tumefactive demyelinating lesions from neoplasm [5]. Generally, the tumefactive lesions showed reduced NAA, increased Cho, lactate and an increased Cho/NAA ratio that reached very high levels similar to that observed in high-grade neoplasms. These MRS findings cannot confidently distinguish tumefactive MS from neoplasm. Rather, the abnormal elevation of glutamate and glutamine peaks is the more critical finding, which is not usually seen in aggressive neoplasms [4, 8]. In addition, the 3D CSI MR spectroscopy is helpful in determining the metabolic profile of the lesion and peri-lesional area which is particularly relevant in MS. In two of our cases, the normal appearing white matter also showed abnormal spectral pattern (Fig. 1 on page 11 G, Fig. 5 on page 12 G).

Dynamic PWI in this study showed diminished rCBV in the lesion centrally and higher rCBV values in the lesion peripherally. PWI does not look extremely helpful in differentiating tumefactive lesions from neoplasm, as tumour with central necrosis may have a similar appearance. DWI findings at the periphery of lesions appear to be significant, notably restricted diffusion on DWI and low ADC represents a zone of active demyelination. This finding was observed in two of the three cases.

Three patients with known MS presented with features suggestive of a neoplastic mass lesion. Initial CT/MR imaging findings made it difficult to differentiate between neoplasm and tumefactive MS. Patients underwent multimodal MRI, with MRS, DWI and PWI. It was found that the near normal NAA, raised glutamate and glutamine peaks and relatively low central rCBV were the more critical findings in distinguishing tumefactive MS from neoplasm. The perivenous enhancement pattern and peripheral restricted diffusion are also useful adjunct features. This case series highlights that tumefactive MS is a diagnostic challenge and many centres proceed to early biopsy, which may be followed by unnecessary surgery or radiotherapy. Careful interpretation of conventional MRI features and combining findings from MRS, DWI and PWI helps to increase diagnostic confidence.

Images for this section:
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Personal information

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References