TITLE

Magnetic Resonance Imaging Features of Gemistocytic Astrocytoma

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IRB Statement

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Short Running Title

MRI Features of Gemistocytic Astrocytoma

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ABSTRACT

Introduction

Gemistocytic astrocytoma is the second most common subtype of World Health Organization grade 2 astrocytoma, but has a worse prognosis than other grade 2 lesions. We aim to describe the MR imaging features of histopathologically proven gemistocytic tumours.

Methods

Ethics approval was obtained from both institutions. Patient consent was not required for this retrospective study. We reviewed MR imaging findings of 16 consecutive cases of histopathologically proven gemistocytic astrocytoma and anaplastic astrocytoma with gemistocytic features.

Results

Average patient age was 48 years, with a 3:1 male to female ratio. Based on our series, the typical appearance of a gemistocytic astrocytoma is a large, heterogeneous mass most commonly supratentorial and lobar. Regions of cyst formation, partial signal suppression on FLAIR images and contrast enhancement are all common features. Additionally, contrary to previous literature that describes gemistocytic astrocytoma as a purely supratentorial lesion, we present two cases of gemistocytic astrocytoma involving the brainstem.

Conclusions

The possibility of gemistocytic astrocytoma should be considered in patients presenting with large heterogeneous tumours that have regions of cyst formation, partial FLAIR suppression and contrast enhancement. This may be especially useful in reconciling a lesion with high-

grade MR imaging features with low grade histopathology. An infratentorial location does not preclude the diagnosis of gemistocytic astrocytoma.

KEYWORDS

Astrocytoma; Brain Neoplasms; Gemistocytic Astrocytoma; Magnetic Resonance Imaging; Radiology

INTRODUCTION

Although gemistocytic astrocytomas are the second most common histological subtype of diffuse astrocytoma behind fibrillary astrocytoma, they are relatively uncommon, accounting for 8 to 29% of all such tumours.[1-6] They are histologically characterized by a significant population of gemistocytic astrocytes on a background of fibrillary astrocytes. Initially thought to be reactive cells, it has since been proven that the gemistocytes are neoplastic, sharing a p53 mutation with other neoplastic astrocytes.[7, 8]

The current World Health Organization (WHO) classification for gemistocytic astrocytoma is grade 2. However, a 1991 study by Krouwer et al. showed that prognosis for astrocytoma with a gemistocytic component was the same irrespective of a background of fibrillary (WHO grade 2) or anaplastic (WHO grade 3) cells, and that as little as 5% gemistocyte tumour cells is sufficient to negatively impact prognosis.[9] It has thus been proposed that all gemistocytic astrocytoma be clinically managed as grade 3 anaplastic astrocytoma, and potentially even reclassified.[9] Given the well-known limitations of sampling error in the histological assessment of astrocytomas, being able to prospectively suggest the diagnosis based on imaging could alter management.[10]

While there have been several studies analysing histopathological features of these tumours, there is a paucity of literature on the radiological appearance.[11] What literature is available is limited to single case reports and one clinico-pathologically focused study that briefly describes only some imaging findings.[4, 12, 13] These publications, as well as anecdotal experience, suggest that gemistocytic astrocytomas have significantly different imaging features to the more common diffuse fibrillary astrocytomas.

We aim to describe the MR imaging features of histopathologically proven gemistocytic astrocytomas, and identify common or specific findings.

METHOD

Patient Population

Ethics approval was obtained from both institutions. Patient consent was not required for this retrospective study. Patients were identified by a search of histopathology reports at two tertiary hospitals for the keywords "gemistocyte" and "gemistocytic". The search encompassed from 2007 (the introduction of the PACS at these institutions) to 2014. All grade 2 or grade 3 astrocytomas with a diagnosis of gemistocytic astrocytoma were included. Astrocytomas with a reported component of gemistocytic astrocytes were also considered for review, regardless of whether they were classified as gemistocytic astrocytomas in the final diagnosis. 27 cases were identified for initial analysis. Patient demographic information was also collected.

Pathology Review

Cases were reviewed independently by two neuropathologists with 32 and 12 years experience, who were aware of the purpose of the study. Tumour grade using WHO criteria was also assessed. The pathology specimens were assessed to confirm the presence of gemistocytes and to quantify the percentage of gemistocytic, fibrillary and protoplasmic astrocytes. Disagreement was resolved by consensus. It was determined that any tumour with <5% gemistocytes could not be considered a gemistocytic astrocytoma, and would be excluded. No cases were excluded for this reason. From the initial 27 cases, 16 were found to consist entirely of gemistocytes and fibrillary astrocytes. Of the remaining 11 cases, 10 were determined to be mixed gemistocytic/protoplasmic astrocytoma, and one was felt, in retrospect, to represent a WHO grade 4 tumour. As both these entities are known to have heterogeneous imaging appearances, these patients were excluded.

Imaging Sequences

Seven patients were scanned on 1.5T Signa Horizon Lx (General Electric, Milwaukee, WI). Six patients were scanned on a 1.5T Magnetom Avanto (Siemens Medical Solutions, Erlangen, Germany). Two patients were scanned on a 1.5T Signa Horizon Echospeed Plus (General Electric, Milwaukee, WI). One patient was scanned on a 3T TIM TRIO (Siemens Medical Solutions, Erlangen, Germany). Exact protocols varied by machine, and evolved over time. Two patients had only post-contrast T1 weighted images (T1WI) volumetric studies available, one patient did not have any post contrast sequences and one patient had dual-echo imaging rather than T2 weighted images (T2WI) and fluid attenuation inversion recovery (FLAIR). The remaining 15 patients all had T2WI (repetition time (TR)/echo time (TE) = 3360-6400 / 93.62-163), FLAIR (TR/TE = 8000-9002 / 87 – 137.50) and pre- and

post-contrast T1WI (TR/TE = 440-640 / 7.38-20). T2* was available for 15 patients and diffusion weighted imaging (DWI) was available for 13 patients.

Imaging Review

All cases were reviewed independently by two neuroradiologists with 21 and 7 years experience. The reviewers were aware of the purpose of the study but blinded to histopathological details and patient identity. Disagreement was resolved by consensus. The cases were assessed for tumour size (axial T2/FLAIR signal abnormality), location, midline and cortex involvement, signal characteristics, FLAIR suppression, contrast enhancement, apparent diffusion coefficient (ADC) of enhancing and non-enhancing regions, and susceptibility.

FLAIR suppression was defined as signal reduction compared to the T2 images, but less than cerebrospinal fluid (CSF). Tumour regions that suppress to the same degree as CSF were described as cystic regions. Midline involvement was determined if any part of the tumour extended into the corpus callosum, anterior or posterior commissures, or brainstem on FLAIR or T1 post-contrast images. Susceptibility was defined as loss of signal on T2* images.

RESULTS

Patient Population

The mean age of our patients was 50 years (48 years for grade 2, 51 years for grade 3), with an age range of 29 to 70 years (37 to 55 years for grade 2, 29 to 70 years for grade 3). Grade 2 tumours had a male predominance, with 6/8 (75%) cases, while in grade 3 tumours, only 3/8 (38%) cases were in male patients.

Pathology Review

Half (8/16) of the tumours were grade 2, compatible with a classical diagnosis of gemistocytic astrocytoma. The remaining 8 tumours were grade 3 astrocytomas, classically defined as anaplastic astrocytoma with gemistocytic features. The average percentage of gemistocytes present was 67% (range 20% to 90%) for grade 2 tumours, and 62% (range 10% to 88%) for grade 3 tumours. As mixed tumours (those with protoplasmic components) were excluded, all included tumours were on a background of fibrillary astrocytes.

Imaging Review

The imaging characteristics are presented in Table 1. Grade 2 tumour size ranged from 32 to 73 mm (average of axial diameter), with a similar size range for grade 3 tumours. 6/8 (75%) of grade 2 tumours were supratentorial and lobar, with 2/8 (25%) involving the brainstem, one as the sole site of disease and the other multifocal with supratentorial lesions. All grade 3 tumours were supratentorial, and 7/8 (88%) were lobar with a single grade 3 tumour arising in the thalamus. Both brainstem lesions were diagnosed on biopsy only and histopathological review assigned both as grade 2. Grade 2 tumours showed midline involvement in 5/8 (63%) cases, and 6/8 (75%) showed cortical involvement. For grade 3 tumours, midline involvement was present in 3/8 (38%) cases, and cortex was involved in 7/8 (88%) cases.

All lesions were T1 hypointense. Most (14 patients) had T2WI and FLAIR imaging available. These all showed high T2 signal, the majority of which (6/7 grade 2; 4/7 grade 3) was heterogeneous. In 3/7 (43%) grade 2 tumours and 2/7 (29%) grade 3 tumours, well-defined cystic regions were demonstrated. This usually constituted only a small percentage of the whole tumour (5-25%), although one grade 2 case was predominantly cystic (>75%). 6/7 (86%) grade 2 tumours and 3/7 (43%) grade 3 tumours showed partial FLAIR suppression of ill-defined markedly T2 hyperintense regions.

Enhancement was present in 75% (6/8) grade 2 cases and 57% (4/7) grade 3 cases. The most common enhancement pattern was predominantly peripheral and nodular. Mild or avid enhancement was seen in equal numbers.

Diffusion restriction was infrequently seen, present in only 2/8 (25%) grade 2 cases, and 2/7 (29%) grade 3 cases. ADC was lower in enhancing, solid regions of tumour compared to non-enhancing areas. No susceptibility was seen on T2* images to indicate presence of blood or calcification in any lesion.

DISCUSSION

We present the imaging characteristics of 16 cases of gemistocytic tumours: 8 grade 2 gemistocytic astrocytomas, and 8 anaplastic astrocytomas with gemistocytic features. This retrospective case series is, to the best of our knowledge, the largest and first dedicated attempt to document the MR imaging features of this tumour. While imaging features have been touched upon in other papers, the literature is limited to either case reports or clinico-pathological papers where only some imaging features are discussed.[12-14]

Background

The literature reports that gemistocytic astrocytoma accounts for between 8% and 29% of WHO grade 2 astrocytomas.[1-6] The variability in reported incidence likely results from absence of clear diagnostic criteria. The percentage of gemistocytes required to give the diagnosis has not been clearly defined. Historically, an arbitrary limit of at least 20% gemistocytes has been used to define this lesion, with some studies further subcategorizing tumours with more than 60% gemistocytes as, somewhat non-intuitively, "pure gemistocytic astrocytomas".[9] It is not known whether the percentage of gemistocytes is prognostically important, with two studies showing no difference in progression-free survival or overall survival between tumours with greater or less than 20% gemistocytes.[8, 13] On the other hand, a study by Watanabe et al has shown more rapid progression in tumours with as little as 5% gemistocytes.[15]

Gemistocytic astrocytomas are currently considered a WHO grade 2 lesion. The presence of anaplasia precludes the classical diagnosis, with tumours demonstrating anaplasia being defined as anaplastic astrocytoma regardless of the percentage of gemistocytes.[11] Despite this WHO classification, gemistocytic astrocytomas have a worse prognosis than other low-grade gliomas, with several studies showing higher recurrence and progression rates[2, 5] and worse overall survival.[1, 4, 6] Conversely, grade 2 gemistocytic astrocytomas and grade 3 anaplastic astrocytoma with gemistocytic features have been shown to have similar survival.[9]

Given the questions surrounding impact on survival in the different classifications of gemistocytic tumours, we chose to examine the imaging features of both grades of tumour. Our results show no difference in MR characteristics between grade 2 and grade 3 lesions, which may be seen as further evidence of blurring of the distinction between grade 2 gemistocytic astrocytomas and anaplastic astrocytoma with gemistocytic features.[9] Regardless, the poorer prognosis of gemistocytic astrocytoma relative to other grade 2 lesions highlights the value of prospective diagnosis on imaging for treatment planning, especially given the well-known limitations of sampling error and inter-observer variability in histological assessment of gliomas.[10]

Patient Population

Patients diagnosed with gemistocytic astrocytomas have been reported to be older than those with other diffuse astrocytomas, with an average age at diagnosis in the 40s, approximately 10 years older than those with other diffuse low-grade gliomas.[1, 4] The demographics of patients in our study conforms to previous literature, with an average age of

48 years. While some authors have postulated that this older age may contribute to the worse prognosis in gemistocytic astrocytomas, as age is a strong independent poor prognostic factor in astrocytoma,[4] other studies show that the prognosis remains worse than for fibrillary tumours even when stratified for age.[1]

Gemistocytic astrocytomas also have a higher male predominance than other diffuse astrocytomas, with a 3:1 male to female ratio, compared with 1.5:1 for fibrillary astrocytoma.[4, 9] This is confirmed with our gemistocytic astrocytomas, though we showed a female predominance in anaplastic astrocytoma with gemistocytic features, possibly due to small sample size.

Imaging Features

Gemistocytic astrocytoma has historically been described as exclusively supratentorial and most commonly found in the frontal lobes.[9] This lobar distribution follows many supratentorial neoplasms, and likely reflects nothing more than the larger size of the frontal lobe compared to other lobes. We also describe two cases where gemistocytic astrocytoma involved the brainstem (Figures 1 and 2). In one case, this was the sole location of disease, and in the second there was also multifocal frontal lobe disease. Both cases were grade 2 lesions (classic gemistocytic astrocytoma). Search of the literature reveals no previous cases of brainstem gemistocytic astrocytoma.

WHO grade 2 diffuse fibrillary astrocytomas are described in the literature as relatively homogeneous T2 hyperintense lesions involving both grey and white matter.[16-18] In contrast, all but one of our gemistocytic astrocytomas showed signal heterogeneity on T2 weighted imaging.

While enhancement is not a feature of grade 2 fibrillary astrocytomas, it has been noted in some grade 2 protoplasmic astrocytomas and grade 2 oligoastrocytomas.[16-19] When present in these lesions, however, it is usually only mild.[19, 20] Our finding of frequent (75%) enhancement (Figure 3), which is as often avid as it is mild, could result in gemistocytic astrocytoma being mistaken for a higher grade lesion on imaging, and if not recognized, potentially lead to the belief that lower histological grade was due to under-sampling.[10] As such, knowledge that the presence of gemistocytes is frequently associated with significant enhancement will help in reconciliation of imaging and histological findings.

In contrast, grade 4 glioblastomas frequently have complete peripheral nodular contrast enhancement, surrounding central areas of necrosis.[21, 22] Although contrast

enhancement was common in gemistocytic astrocytomas, it is often mild, and when more pronounced did not have a continuous peripheral ring.

Our finding of 43% of cases showing well-defined cystic regions (Figure 4) supports the study of Yang et al. (2003), which demonstrated regions of cystic change in 44% of their 25 selected cases. This is a feature more commonly associated with higher grade tumours,[22] but we show it to be a common finding in gemistocytic astrocytoma.

Partial FLAIR suppression of ill-defined markedly T2 hyperintense regions (Figures 4 and 5) absent in fibrillary astrocytomas, has been described in protoplasmic astrocytomas and dysembryoplastic neuroepithelial tumours (DNETs).[19, 23] It is not a described feature in glioblastomas, even when the tumour has a significant non-enhancing component.[24]

Histopathologically, gemistocytes are described as cells with "voluminous, homogeneous, slightly eosinophilic cytoplasm with few branching processes and an eccentric nucleus"[25] (see Figure 6 for an example). Although this cellular feature may in part account for FLAIR suppression, this imaging feature is encountered in other lesions without gemistocytes, so it is likely the other factors are contributing, likely within the extracellular milieu. Future studies aimed at determining a histopathological-radiological correlation for FLAIR suppression would be instructional.

Diffusion restriction was seen in less than half of cases. This features has previously been ascribed to increased cellularity in gliomas[22], and we noted lower ADC values in enhancing regions of tumour compared to non-enhancing regions, suggesting the enhancing regions have higher cellularity.

Despite this study being the largest series of gemistocytic tumours reported in the radiology literature, a limitation is the small number of cases. Our finding of no difference on MR imaging between grade 2 and 3 lesions, for example, may merely represent small sample size. A minority of our cases were diagnosed on biopsy rather than resection, and the possibility of non-representative biopsies must also be acknowledged. This is particularly important with regard to the two brainstem gemistocytic astrocytomas we report, both diagnosed on biopsy alone.

Conclusions

Gemistocytic astrocytoma is a tumour with a worse prognosis than other WHO grade 2 astrocytomas. Prospective diagnosis may affect management, and help reconcile differences between histopathological grade and radiological appearance. Based on our series of both classical and grade 3 gemistocytic lesions, the possibility of gemistocytic tumour should be

considered in patients presenting with large, heterogeneous lesions that have regions of cyst formation, partial FLAIR suppression and contrast enhancement.

COMPETING INTERESTS

None to disclose.

FUNDING INFORMATION

None to disclose.

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Fig. 1 – 72-year-old-female with WHO grade 2 gemistocytic astrocytoma. T2 (a), FLAIR (b) and T1WI post-contrast axial (c) and coronal (d) images, showing an enhancing mass in the midbrain and pons. Note central FLAIR suppression. This patient also had lesions in both frontal lobes (not shown).

Fig. 2 – 38-year-old female with WHO grade 2 gemistocytic astrocytoma. T2 (a), FLAIR (b) and T1WI post-contrast axial (c) and coronal (d) images, showing a small, enhancing lesion in the brainstem (medulla oblongata, arrow).

Fig. 3 – T1-weighted images post contrast, indicating different patterns of enhancement (arrows). (a) Peripheral nodular enhancement in a 37-year-old male with WHO grade 2 gemistocytic astrocytoma. (b) Heterogeneous region of enhancement in a 29-year-old male with WHO grade 3 anaplastic astrocytoma with gemistocytic features.

Fig. 4 – 37-year-old male with WHO grade 2 gemistocytic astrocytoma. T2WI (a) and FLAIR (b) images, showing regions of cyst formation (arrow) and ill-defined partial FLAIR suppression (asterisk).

Fig. 5 – 29-year-old male with WHO grade 3 anaplastic astrocytoma with gemistocytic features. T2WI (a) and FLAIR (b) images, showing regions of cyst formation (arrow) and ill-defined partial FLAIR suppression (asterisk).

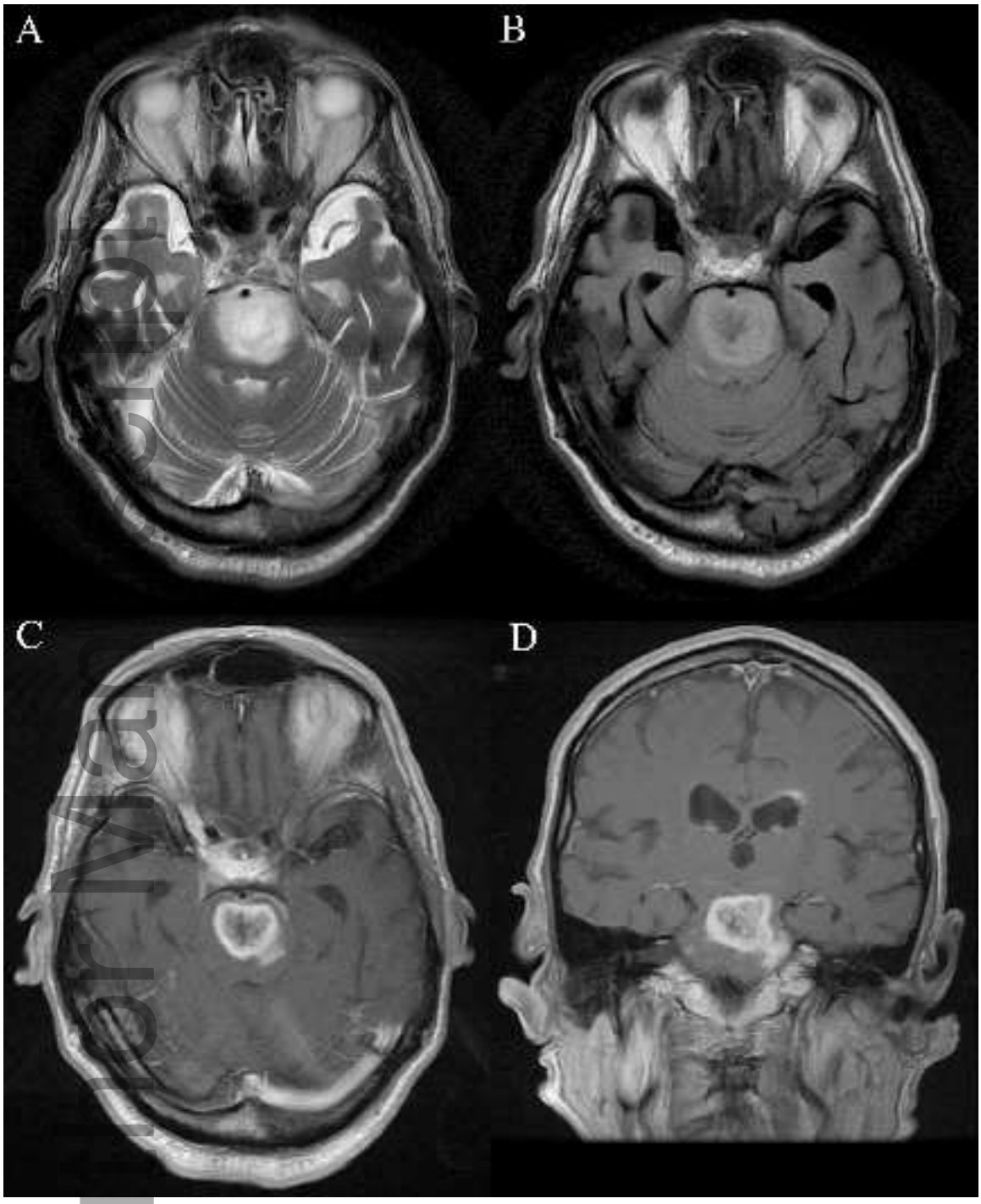
Fig. 6 – 32-year-old female with WHO grade 3 anaplastic astrocytoma with gemistocytic features. 400 x magnification hematoxylin and eosin (H&E) stain showing the typical appearance of neoplastic gemistocytes, with large volume pink-staining cytoplasm and eccentric nuclei (arrows).

Table 1: Imaging features by tumour WHO grade.

Feature	Grade 2 Gemistocytic astrocytoma (n=8)	Grade 3 Anaplastic astrocytoma with gemistocytic features (n=8)
Location	Frontal (5/8), temporal (1/8),	Frontal (3/8), frontotemporal

	brainstem (1/8), multifocal* (1/8)	(3/8), parietal (1/8), thalamus (1/8)
Cortex	Involved (6/8), uninvolved (2/8)	Involved (7/8), uninvolved (1/8)
Midline	Involved (5/8), uninvolved (3/8)	Involved (3/8), uninvolved (5/8)
Size - mean diameter (range)	53 mm (32 to 73 mm)	56 mm (36 to 70 mm)
T1 signal	hypointense (8/8)	hypointense (7/7)
T2 signal	hyperintense (7/7)	hyperintense (7/7)
T2 characteristics	heterogeneous (6/7), homogeneous (1/7)	heterogeneous (4/7), homogeneous (3/7)
Cystic regions (percentage of total tumour)	None (4/7), 5-25% (2/7), >75% (1/7)	None (5/7), 5-25% (2/7)
Ill-defined FLAIR suppression	Yes (6/7), No (1/7)	Yes (3/7), No (4/7)
Enhancement	None (2/8), Mild (3/8), Significant (3/8)	None (3/7), Mild (2/7), Significant (2/7)
Pattern of enhancement	Peripheral nodular (4/6), Solid region (1/6), Wispy (1/6)	Heterogeneous region (2/4), Peripheral Nodular (1/4), Wispy (1/4)
Diffusion restriction	No (4/6), Yes (2/6)	No (5/7), Yes (2/7)
ADC of non-enhancing region – mean (range)	1590 (1535 to 1663)	1107 (554 to 1434)
ADC of enhancing region – mean (range)	1099 (900 to 1310)	983 (850 to 1115)

Note. *multifocal case involved both frontal lobe and brainstem; ADC are expressed as 10^{-6} mm^2/s



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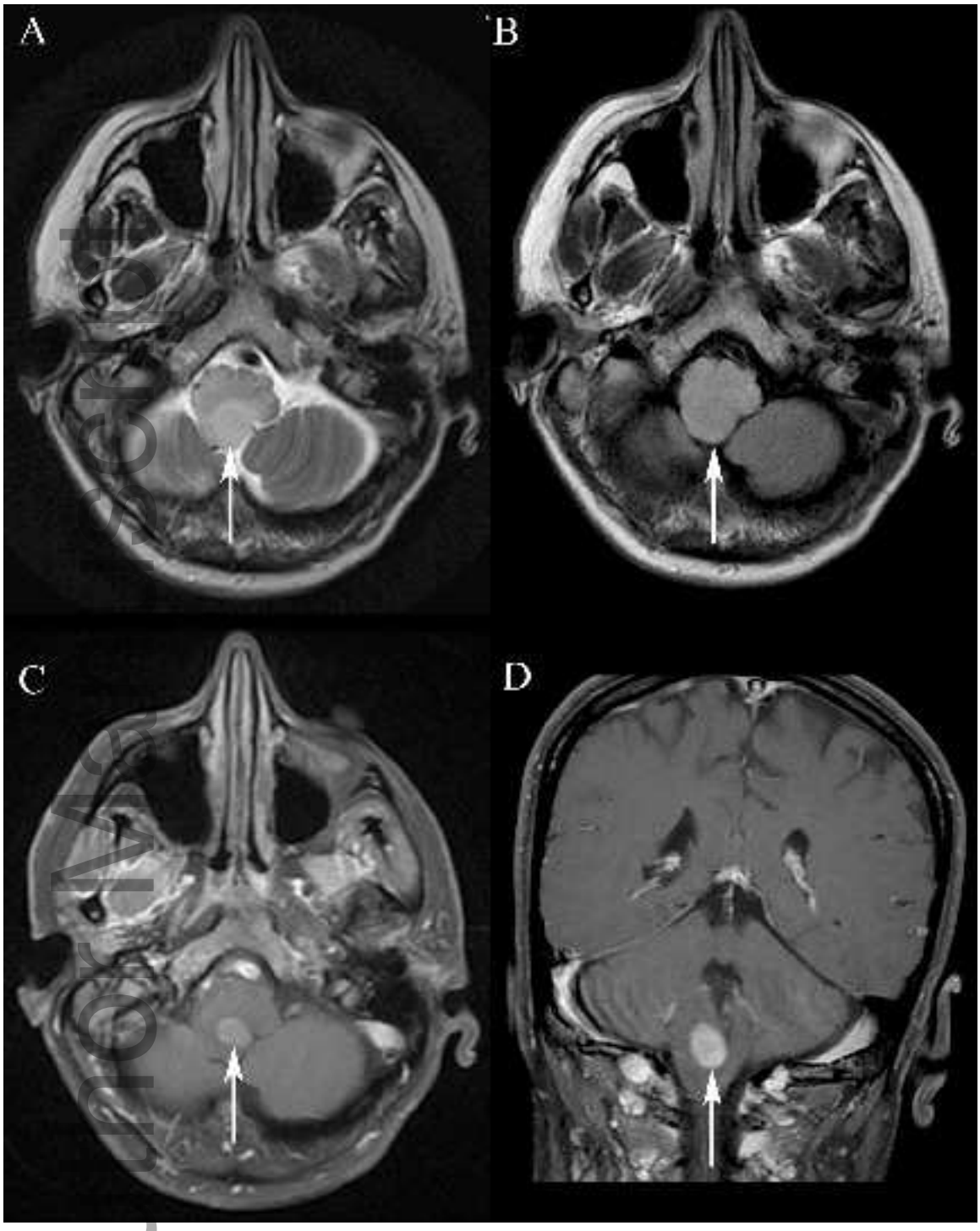

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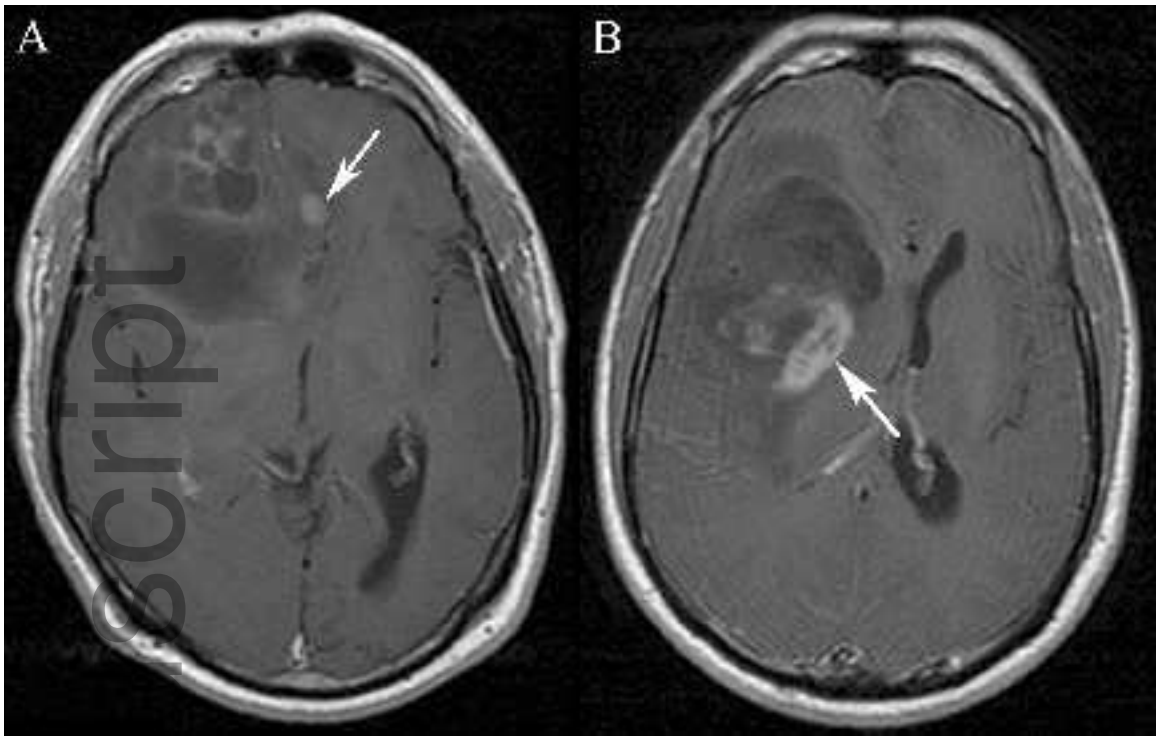

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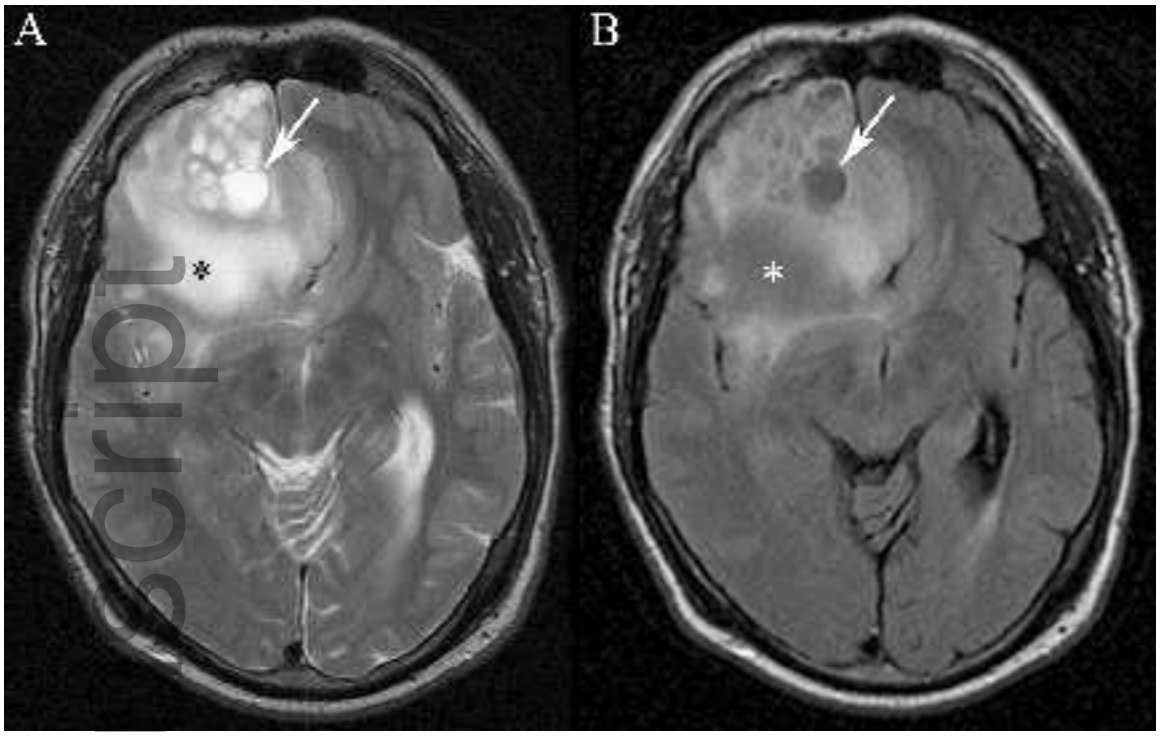

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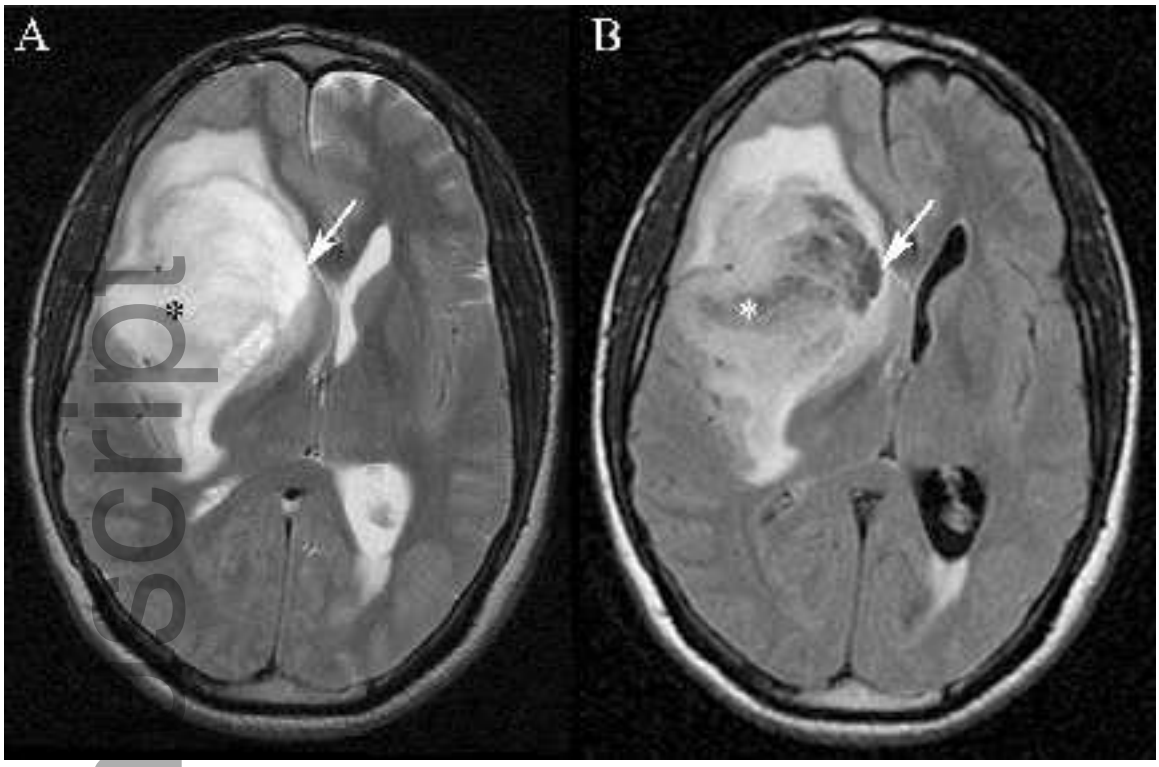

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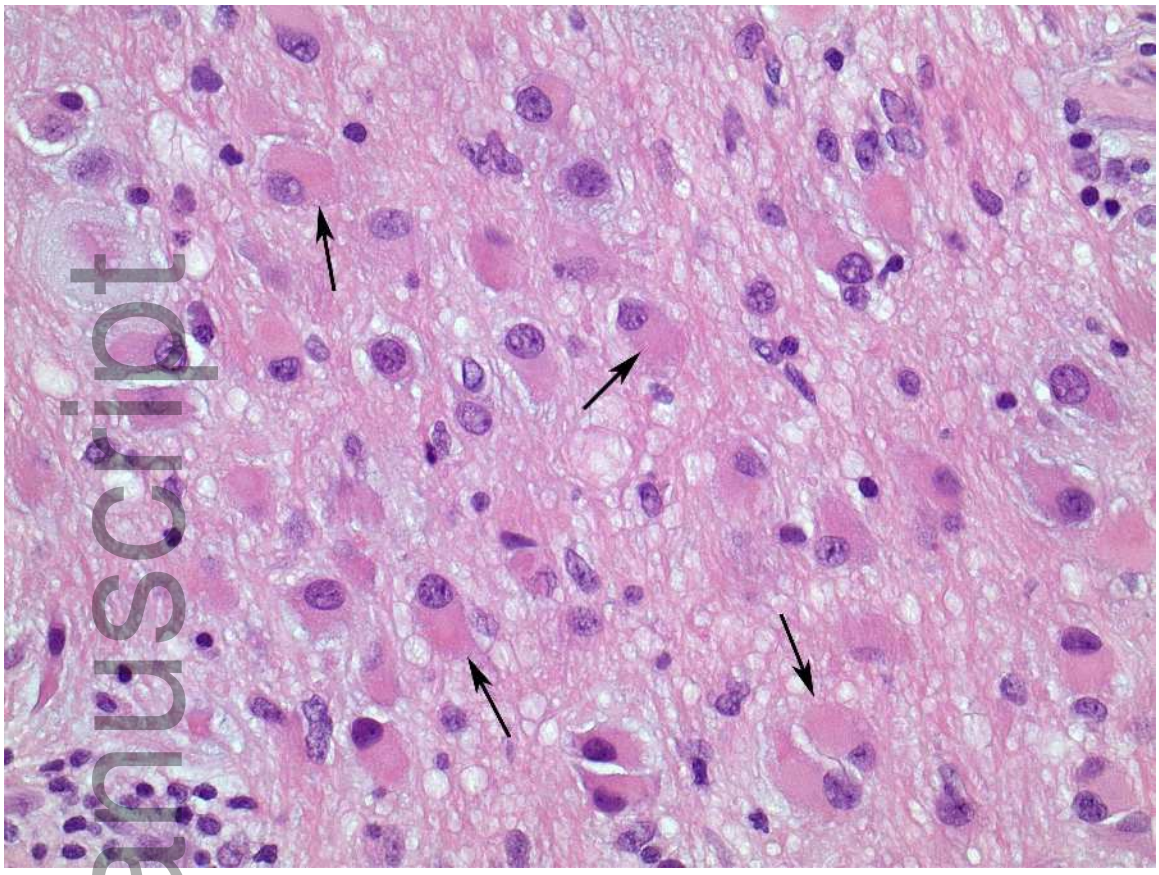

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