TITLE: Can MRI differentiate between ring-enhancing gliomas and intra-axial abscesses?

AUTHORS: Andrea Carloni[a], Marco Bernardini[a,b], Chiara Mattei[a], Angela Vittoria De Magistris[a], Francisco Llabres-Diaz[c], Jonathan Williams[c], Rodrigo Gutierrez-Quintana[d], Anna Oevermann[e], Daniela Schweizer-Gorgas[e], Cyrielle Finck[f], Isabelle Masseau[f], Valentina Lorenzo[g], Annalisa Sabatini[h], Barbara Contiero[b], Swan Specchi[a]

AFFILIATIONS:

[a]Diagnostic Imaging department, Veterinary Hospital "I Portoni Rossi" Anicura Italy, Zola Predosa (BO), Italy.

[b]Department of Animal Medicine, Production and Health, Clinical Section, University of Padua, Legnaro, Padua, Italy.

[c]Royal Veterinary College, Hatfield, UK.

[d]School of Veterinary Medicine, College of Medical Veterinary and Life Sciences, University of Glasgow, UK.

[e]Division of Neurological Sciences, Vetsuisse Faculty, University of Bern, Bern, Switzerland.

[f]Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Montreal, Saint-Hyacinthe, Qc, Canada.

[g]Neurología Veterinaria, Getafe, Madrid, Spain.

[h]Veterinary Hospital "Gregorio VII", Roma, Italy.

CORRESPONDENCE:

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ABSTRACT

Gliomas may appear as expansile ring-enhancing masses, mimicking the radiological appearance of intra-axial abscesses. The aims of this study were to compare the MRI features of ring-enhancing gliomas and intra-axial brain abscesses in dogs and cats and to identify the characteristics that might help differentiate them. For this multicenter, retrospective, and descriptive study inclusion criteria were the following: a) a definitive diagnosis of glioma or abscess based on cytological or histopathological examination following CSF collection or surgical biopsy/necropsy, respectively; b) MRI study performed with a high or low field MRI scanner, including a same plane T1W pre- and post-contrast, a T2W and a T2 FLAIR sequence in at least one plane. ~~; b) confirmed diagnosis of glioma or abscess through brain histology, CSF analysis surg~~Delayed T1W post-contrast and T2*W GE sequences were also evaluated when available.

A total of 31 cases met the inclusion criteria. Sixteen patients were diagnosed with ring-enhancing gliomas and 15 with intra-axial abscesses. A homogenous signal on T1W or T2W sequences, a T2W or T2*W GE peripheral hypointense halo and, an even enhancing capsule were significantly associated with brain abscesses. A progressive central enhancement on T1W delayed post-contrast sequences was correlated with ring-enhancing gliomas. Despite identifying multiple overlapping MRI features between ring-enhancing gliomas and brain abscesses, some of the features helped prioritizing the MRI diagnosis. In particular, the presence of a homogeneous T1W or T2W signal intensity, of a T2W or T2*W GE peripheral hypointense halo and an even enhancing capsule suggested brain abscess. The central progression of the enhancement on delayed T1W post-contrast sequences was indicative of glioma.

**Commented [LDF1]:** Even or continuous better than regular?

**Commented [CF2]:** I also find the term “regular” not that precise. You would also have to define the term in you MM

## INTRODUCTION

Gliomas are primary neuroepithelial tumors accounting for approximately 35–37% of all primary brain tumors in dogs. sneyder 2006, Song 2013) Glial tumors are less common in cats, representing approximately 8% of feline primary brain tumors.(Troxel 2003) Common MRI features of gliomas include single, intra-axial, T1-weighted (T1W) iso- to hypointense and T2-weighted (T2W) iso- to hyperintense to normal brain parenchyma cyst-like or necrotic lesions, with variable distribution and degree of contrast enhancement. (Sneyder 2006, hect 2018, wisner 2011, young 2011, Bentely 2013) Intratumoral hemorrhages component have also been reported. (Benteley 2013)

Brain abscesses are uncommon in companion animals and may occur via a hematogenous entry of bacteria, direct invasion/contiguity, or contamination of cerebrospinal fluid. (Thomas 1999, Sonneville 2017, Radaelli 2002, Costanzo 2011, Klopp 2000, Mateo 2007, Rosenblatt 2014, Seiler 2001) A brain abscess begins as a localized area of neutrophilic encephalitis and, if untreated, may progress into liquefactive necrosis containing viable and degenerate neutrophils (pus) surrounded within 1 to 2 weeks by a well-vascularized fibrovascular capsule. (Thomas 1999, Sonneville 2017) On MRI, a brain abscess has been reported as a focal, T2W hyperintense and T1W hypointense lesion compared to normal brain parenchyma, with a necrotic non-enhancing center, surrounded by a thick and strongly contrast-enhancing peripheral rim.(Costanzo 2011, Klopp 2000, Mateo 2007, Seiler 2001, Bach 2007)

A recent review in veterinary literature reports up to 45% of gliomas having partial or complete ring-enhancement;Miller 2019 therefore, gliomas may appear as expansile ring-enhancing masses, mimicking the radiological appearance of intra-axial abscesses Huisman 2009. In human medicine, multiple MRI studies using specific sequences have attempted to find unique characteristics to distinguish between ring-enhancing gliomas and abscesses. A hypointense peripheral capsule on T2W images caused by paramagnetic free radicals within

**Commented [LDF3]:** To normal parenchyma

**Commented [AC4R3]:** Added

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**Commented [AC6R5]:** Added

**Commented [LDF7]:** same

**Commented [AC8R7]:** Added

**Commented [RGQ9]:** If any previous papers report the percentage of gliomas that present as ring-enhancing masses, it will be nice to add the information.

**Commented [AC10R9]:** We add a reference, Miller 2019 on Frontiers, Table 1

phagocytic macrophages, often associated with susceptibility artifact in T2W gradient echo (T2*) and to a double rim sign in susceptibility-weighted imaging (SWI), is considered a distinguishing feature of brain abscesses in humans.(Haimes 1988, Toh 2012) Abscesses commonly show restricted diffusion in diffusion weighted imaging (DWI) while gliomas usually do not.(kim 1998, Toh 2011, Chiang 2009, Huisman 2009) However, overlapping imaging features have been reported.(Reddy 2006, Reiche 2010, Hakymez 2005)

Since the two diseases require very different treatment and have a different prognosis(Costanzo 2011,Bersan 2020, Bilderback 2009, Miller 2019), a correct imaging interpretation is paramount.

The aims of this study were to compare the MRI features of confirmed ring-enhancing gliomas and intra-axial brain abscesses in dogs and cats and to identify the imaging features that might help to differentiate them.

**Commented [LDF11]:** I think usually editors prefer past tense but happy if you want to use present tense throughout, just check.

**Commented [AC12R11]:** We check thanks. There should be only past tense now.

## MATERIALS AND METHODS

### CASE SELECTION CRITERIA

This was a multicenter, retrospective, descriptive study. All animals included were client-owned and underwent MRI examinations of the brain. Previous informed written consent was obtained from all dog owners. All the procedures performed complied with the European legislation “on the protection of animals used for scientific purposes” (Directive 2010/63/EU).

The databases of the Veterinary Hospital “I Portoni Rossi” Anicura Italy, the Veterinary Teaching Hospital of the University of Bern, the Royal Veterinary College, the University of Glasgow, the University of Montreal, the Veterinary Clinic “Neurología Veterinaria” and the Veterinary Hospital “Gregorio VII” were searched for dogs and cats diagnosed with a single ring-enhancing intra-axial lesion. Patients’ age, sex, and breed were recorded.

Inclusion criteria were the following: (1) a definitive diagnosis of glioma or abscess based on cytological or histopathological examination following CSF collection or surgical biopsy/necropsy, respectively; (2) a MRI study performed with a high or low field MRI scanner, including at least a same plane pre- and postcontrast T1W and a T2W sequence in at least one plane and at T2 FLAIR sequence in any plane. If available, T2*W GE, DWI/ADC, SWI and delayed postcontrast T1W sequences were analyzed.

Because the aim of the study was to describe the MRI features of brain abscesses and to compare them with ring-enhancing gliomas in doubtful cases, the presence of MRI changes related to bite wounds were recorded, but not considered as imaging criteria.

IMAGE ANALYSIS

Images were analyzed by a board-certified radiologist (SS), a board-certified neurologist (MB) and a second-year resident in diagnostic imaging (AC) not blinded to the final diagnosis. The final decision on the imaging characteristics was reached on a consensus basis. The studies were randomly reviewed using a DICOM (i.e., Digital Imaging and Communications in Medicine) viewer program (OsiriX DICOM viewer, Pixmeo, Geneva Switzerland). The three observers were asked to fill in a pre-defined standardized commercially available spreadsheet (Microsoft Excel 2020, Microsoft, Redmond, Wash). The following MRI features were assessed: T1W and T2W signal heterogeneity/homogeneity as well as the intensity (hypo-, iso-, hyper-) of the signal compared to normal parenchyma on the same sequences; presence of a peripheral hypointense halo in T2W sequences compared to contents of the lesion; presence of a T2 FLAIR attenuated component within the lesion; presence and grade (0, no; 1, mild; 2, moderate; 3, severe) of perilesional white matter edema based on subjective evaluation; pattern of ring enhancement (even/uneven); presence of progressive central enhancement on delayed post-contrast sequences (delayed post-contrast

**Commented [LDF13]:** Different to the abstract

**Commented [AC14R13]:** We added it to the abstract

**Commented [CF15]:** Did you analyse ADC images in conjunction with the DWI images?usually the analysis is done in combination to avoid any T2 shine through confusion. I would specify ita s “DWI/ADC”

**Commented [AC16R15]:** Yes we always analyzed DWI and the corresponding ADC map. Now in the text we put DWI/ADC

**Commented [IM17]:** Any reason for not looking at precise location of lesion and size?

**Commented [SS18R17]:** No particular reason, we didn’t consider it as criterion

**Commented [LDF19]:** Compared to….

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**Commented [LDF21]:** May be better low signal? Or hypointense to 1)contents of the lesion or 2) surrounding parenchyma

**Commented [CF22R21]:** I would have the same comment. I know a lot of people use the terms hypointense or hyperintense without any more precision but technically it is hypo or hyperintense to something in reference. Alternatively you could use the terms low or high signal alone.

**Commented [CF23]:** Was this grade subjective or based on previous litterature? I think you need to specify it (for example the grade was established based on a scoring system established byt he authors/adaptated from previous litterature

**Commented [AC24R23]:** We subjectively graded the vasogenic edema reaching a consensus. I clarify in the text that point.

enhancement was assessed in different planes if the same plane was not available) and the ratio between lesion diameter and maximum capsule thickness in the immediate T1 post contrast images. In cases in which T2*W GE sequences, DWI or SWI were available, additional data were collected such as the presence of susceptibility artifact (i.e., hemorrhage) and a hypointense peripheral halo compared to lesion content in T2*W GE sequences; the presence of abnormal diffusion restriction in DWI/ADC; the presence of "dual-rim sign" (e.g., defined as two concentric rims at lesion margins with the outer one being hypointense and the inner one hyperintense relative to cavity contents) in SWI as described by Toh et al in 2012.

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**Commented [AC26R25]:** Added

**Commented [CF27]:** diffusion restriction?
You need to analyse the ADC conjointly with the DWI to assess for diffusion restriction and identify T2 shine through artefacts so I would precise "DWI/ADC images" instead of just "DWI"

STATISTICAL ANALYSIS

Count data regarding the abscesses/gliomas diagnosis were crossed referenced the MRI findings to obtain contingency tables. Chi-square test was applied to analyse data, using Yates correction for 2x2 contingency tables and Fisher's exact test when frequencies inside tables were less than 5. When a significant association ($P<0.05$) was found between an MRI qualitative predictor and abscess/gliomas classification, the relative risk and 95% confidence interval (95%CI) were calculated.

The ratio between the lesion diameter and capsule thickness in the immediate T1 post-contrast sequences was analyzed using a ROC approach to identify the cut-off that could best discriminate between abscesses and gliomas. The threshold was calculated using the Youden criterion. All analyses were performed with commercial software (MedCalc, Software Ltd, Ostend, Belgium).

## RESULTS

A total of 31 cases met the inclusion criteria. Sixteen patients were diagnosed with ring-

**Commented [IM28]:** How were they diagnosed? Necropsy? Biopsy? CSF cytology?

**Commented [AC29R28]:** We added these informations.

enhancing gliomas through necropsy (15/16) or surgical biopsies (1/15); Intra-axial abscesses were diagnosed in 15 patients through necropsy (5/15), CSF analysis (7/15) and surgical biopsies (3/15). Within the abscess group 6/15 had evidence of bite wounds/perforating lesions visible as temporal muscle myopathy and calvarial focal defects in continuity/contiguity with the intra-axial mass.

MRI scanning techniques were similar for each institution. The coil selection was based on individual patients and the availability of the single institution. All the animals were imaged in sternal recumbency, under general anesthesia.

MRI studies were performed with both low- and high-field MRI scanners; specific characteristic of each MRI scanner are listed in Appendix 1.

T2*W GE sequences were available in 13 cases of ring-enhancing glioma and in 9 cases of intra-axial abscessation. DWI sequences were obtained in 6 cases with ring-enhancing glioma and in one patient with brain abscess. SWI was available in only one patient with ring-enhancing glioma.

Delayed T1W post-contrast sequences were available in 12 glioma cases and on 10 intra-axial abscess cases.

In the ring-enhancing gliomas group there were 13 dogs and 3 cats. The canine breeds represented in the study were Boxer (n = 3), French Bulldog (n = 2), Labrador Retriever (n = 2), Jack Russell terrier (n = 2), Lhasa Apso, Boston Terrier, Springer Spaniel and mixed-breed (n = 1 each). Two Domestic short-haired and 1 Sacred Birman cat represented the feline group. Of the 13 dogs, 6 were males (4 neutered) and 7 females (3 spayed). The 3 cats were 2 spayed females and 1 male. The mean age was 7 years (range: 5-11) for dogs and 9 years (range: 5-15) for cats.

In the intra-axial abscesses group, there were 10 dogs (3 mixed-breed, 1 Boxer, 1 Staffordshire Bull Terrier, 1 West Highland White Terrier, 1 Border Terrier, 1 Miniature

**Commented [CF30]:** Did you get these numbers/repartition within groups by "chance" after all the pertinent cases from the institutions were included, or did you aim to get roughly the same number of patients in each group and look for additional patients until the number you aimed was reached (or left out some cases in one group if there were too many)? If so you should probably precise it in the MM. If not, please disregard my comment and leave things as they are!

**Commented [SS31R30]:** By chance!

**Commented [IM32]:** Even if this was an inclusion criteria (certain types of sequences), perhaps some details about planes vs. sequences performed in all dogs would be helpful here. Did all dogs have a similar number of sequences?

**Commented [AC33R32]:** The number of sequence was pretty variable. Some institution performed the same sequences on multiple planes and other did not. Some institution obtained FLAIR in dorsal plane and other in transverse and so on…. So, as Swan write in the comment below we would stand by and eventually add it in an addendum in case reviewers will ask

**Commented [IM34]:** What coils were generally used?

**Commented [SS35R34]:** Pretty complicated to add all coils for different patients from different institutions… I would stand by on this one and eventually add it in case reviewers will ask (maybe in an addendum, not within the article)

Schnauzer, 1 Chihuahua and 1 Golden Retriever) and 5 cats (4 Domestic short-haired and 1 Domestic long-haired cat). Of the 10 dogs 4 were males (1 neutered) and 6 females (3 spayed). The 5 cats were 4 neutered males and 1 spayed female. The mean age was 4.9 years old (range: 1-11) for dogs and 8.4 years old (range: 5-12) for cats.

MRI findings of ring-enhancing gliomas and brain abscesses are summarized in table 1.

RING-ENHANCING GLIOMAS *vs.* BRAIN ABSCESSES

Brain abscesses showed a more homogeneous signal on T1W (P = 0.049) and T2W sequences (P = 0.042) compared to ring-enhancing gliomas. A peripheral hypointense halo on T2W (P = 0.005) and T2* (P = 0.046) sequences was significantly associated with brain abscesses rather than ring-enhancing gliomas (Figure 1).

On postcontrast T1W sequences, abscesses showed a more even ring-enhancing capsule compared to the ring-enhancing gliomas (P = 0.002), while ring-enhancing gliomas were more likely to have a progressive central enhancement on T1W delayed postcontrast sequences (P = 0.009) (figure 2 and 3).

Based on the receiver-operating characteristic (ROC) analysis, a cut-off value of >12 in the ratio between lesion diameter and capsule thickness in the immediate T1 post contrast sequences had a 43.75%  sensitivity and 85.71% specificity in the detection of ring-enhancing gliomas.

The overall homogeneity of the lesions, the intensity of the lesions (hyperintense, isointense or hypointense) compared to the gray matter, the presence of a T2 FLAIR attenuating component within the mass, the presence and grade of T2 FLAIR perilesional vasogenic edema, the presence of intralesional susceptibility artefacts, and the ~~restriction to diffuse~~diffusion restriction in DWI/ADC were not statistically significant.

Comparison between groups for MRI characteristics is detailed in Table 2.

**Commented [CF36]:** Diffusion restriction?

**Commented [AC37R36]:** We modified it

## DISCUSSION

Our study showed that ring-enhancing gliomas share several MRI features with intra-axial brain abscesses. However, a homogenous signal on T1W and T2W sequences, a T2W and T2*W GE peripheral hypointense halo, and an even enhancing capsule were more likely associated with brain abscesses. Progressive central enhancement on T1W delayed postcontrast sequences was strongly associated with ring-enhancing gliomas while this feature was only present in a single dog with a brain abscess.

The presence of bite wounds/perforating lesions in continuity/contiguity with an intra-axial mass makes a brain abscess the very most likely differential diagnosis. However, we did not consider them as imaging criteria because we aimed to focus on those MRI findings that can help the clinician in a doubtful clinical situation.

In our cohort of patients, brain abscesses had a significantly more homogeneous signal on T1W and T2W sequences likely reflecting the presence of necrotic/fluid content in the abscess. Costanzo 2011, Klopp 2000, Mateo 2007, Seiler 2001, Bach 2007 In contrast, ring-enhancing gliomas usually showed a more heterogeneous T1W or T2W signal due to the presence of variable content in these tumors, including hemorrhage, necrotic tumor tissue, cysts or altered cellular density. Lipsitz 2003, wisner 2011, young 2011, Bentely 2013, Miller 2019

There was absence of statistical significance in the evaluation of the type of T1 and T2 signal compared to the grey matter in both gliomas and abscesses. This is related to the tumor heterogeneity in gliomas and the variable ratio between cellular/proteins content in abscesses depending on the stage respectively. During their development, abscesses begin as a focal area of encephalitis histologically defined by a perivascular infiltration of neutrophils, lymphocytes, and plasma cells within the brain parenchyma with an ill-defined central necrotic zone composed of inflammatory cells, cellular debris, and microorganisms.

**Commented [IM38]:** The reader doesn't know from reading this sentence if this is meant to refer to literature or to the study. If this refers to the study you might want to consider: Our study showed that ring-encing gliomas share several MRI features with intra-axial brain abscesses.

**Commented [AC39R38]:** We rephrased it

**Commented [OA(40]:** Grade or stage? I guess rather stage

**Commented [AC41R40]:** We put stage

Subsequentely, the necrotic center increases in size and becomes more well defined. As the abscess becomes more chronic the central necrosis decreases and if left untreated and the patient survives, the abscess will heal as a collapsed fibrotic glial scar.[Klopp 2000]

Our study demonstrates a significant correlation between a peripheral hypointense halo on T2W and T2*W GE sequences and brain abscesses. This halo is due to paramagnetic free radicals within phagocytic macrophages and it has already been described in both human and veterinary medicine.[Haimes 1988, Costanzo 2011, Seiler 2001, Bach 2007, Kim 1998, Thomas 1990, Nagendran 2021]. However, in our study this halo was seen in most, but not all the abscesses; moreover, it was also visible in the MRI study of one patient with a glioma. A T2W and T2*W GE peripheral hypointense halo has been described in both veterinary and human literature in several conditions such as gliomas, chronic hematomas, metastases, granulomatous lesions, infarctions, meningiomas, and radiation necrosis. [Haimes 1988, Klopp 2000] Despite its statistical significance, it cannot therefore be regarded as pathognomonic for brain abscesses.

Another MRI finding that statistically correlated with brain abscesses was the presence of an even ~~regular~~ enhancing capsule. This may be explained by the pathophysiology of brain abscesses formation, which includes four different stages: the first two stages represent the "early" and "late encephalitis" phases without collagenous capsule; during stage 3, called "early capsule", there is an initial deposition of collagen at the periphery of the necrotic center is followed by ingrowth of granulation tissue and neovascularization; in the fourth or "late capsule" stage there is complete formation of the capsule surrounding the necrotic center. [Klopp 2000] Ring enhancing gliomas are not truly encapsulated, and the peripheral enhancing portion of the lesion represents expanding neoplastic tissue with microvascular proliferations surrounding a central necrotic core.[Lipsitz 2003] The intrinsic neoplastic nature of this tissue may explain both its uneven peripheral enhancement pattern and the progressive central enhancement noted in 9 out of the 12 T1W delayed postcontrast sequences, that correlated

**Commented [OA(42]:** To my understanding it is the microvascular proliferation (in high grade gliomas) that causes peripheral enhancement. Not the neoplastic tissue itself.

**Commented [AC43R42]:** We added the microvascular proliferation

with ring-enhancing gliomas. In both veterinary and human literature, intra-axial lesions usually show progressively increased conspicuity on delayed postcontrast sequences. Song 1995, Mai-Brain Neoplasia-Hecht, Abstract Carmel Moreover, the presence of tumor angiogenesis along with poorly vascularized peripheral neoplastic tissue surrounding the necrotic center may play a role in the delayed central progression of the enhancement.Lipsitz 2003

In one brain abscess a very mild progressive central enhancement was indeed seen. In this case, immediate and delayed postcontrast T1W sequences were acquired in different planes and the progressive central enhancement may therefore not be real. Other possible explanations are a partial volume artifact due to the capsule's thickness or the presence of a very thick capsule that necessitated more time to enhance completely.

When evaluating the ratio between the lesion diameter and the capsule's thickness in the immediate postcontrast T1W sequences, a cut-off >12 (43.75% sensitivity and 85.71% specificity) can be proposed for the detection of ring-enhancing gliomas. The ~~irregular~~ uneven peripheral enhancement pattern of ring-enhancing gliomas due to the presence of microvascular proliferation compared to the more ~~regular~~ even and smooth capsule of brain abscesses Klopp 2000, Lipsitz 2003 would explain why ring-enhancing gliomas had higher lesion diameter:capsule thickness ratio than abscesses ~~gliomas~~.

T2 FLAIR sequences have been proposed to characterize fluid collections and differentiate fluid-cavitary lesions from other parenchymal T2 high signal lesions. Bentely 2013 Cystic ~~or~~ ~~necrotic~~ regions are typical of canine glioblastoma but can also occur in approximately one-third of low-grade canine gliomas; Lipsitz 2003, Bentely 2013 On the other hand, brain abscesses during their development show a necrotic core that may mimic the signal intensity and the cellular density of a ring-enhancing glioma Klopp 2000, Lipsitz 2003 explaining the lack of statistical significance of an intralesional T2 FLAIR attenuating component in our study.

The grade of the perilesional vasogenic edema was not statistically significant; vasogenic

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**Commented [LDF46]:** check
As before, I think explaining in slightly more detail (or using one of your figures) to show what you mean by regular / irregular

**Commented [OA(47]:** Necrosis does not really occur in low-grade gliomas, as necrosis is one criterium for high grade.

**Commented [AC48R47]:** We remove the word "necrotic".

edema is secondary to the disruption of the blood-brain-barrier (BBB) and represents a nonspecific feature of several brain diseases including neoplasm and infectious disorders[Ho 2012, Patel 2014]. In humans, two patterns of vasogenic edema have been described: type 1 is seen in the immediate vicinity of low-grade and nonglial tumors and is thought to be secondary to parenchymal compression with secondary ischemia and necrosis; type 2 occurs with high-grade glial tumors and is characterized by fingerlike projections reflecting tumor microinvasion causing additional derangements of the BBB.[Ho 2012] Further studies are needed to investigate the relationship between the severity of perilesional vasogenic edema, brain abscesses and low- and high-grade gliomas.

The presence of intralesional T2*W GE susceptibility artifact was observed in 4/13 patients with ring-enhancing gliomas and only in 1/9 with brain abscesses, failing to achieve statistical significance, probably due to the small sample of patients. These susceptibility artifacts were likely consistent with hemorrhage or neovascularization, which are more commonly reported in gliomas. [Lipsitz 2003, wisner 2011, young 2011, Bentely 2013, Weston 2020] A recent article in veterinary medicine describes the presence of neovascularization in 74.1% of intracranial tumors included in the study.[Weston 2020] A fine, linear, and continuous structure may be more likely interpreted as neovascularization, while a signal void usually represents an intralesional hemorrhage. However, in our study, T2*W GE intralesional susceptibility artifacts were seen in one feline patient with brain abscess. These artifacts likely have to be related with hemorrhages secondary to the recent bite wound reported in the medical record.

Only seven MRI studies included a DWI/ADC sequence. This sequence was not included as part of the standard MRI brain protocol for many of the institutions. In patients (n=6) with ring-enhancing gliomas for whom DWI sequence was available, all showed an increased diffusion of the lesion whereas the only patient with a brain abscess showed, instead, an abnormal restriction to diffusion (figure 3). These findings agree with what is reported in

**Commented [OA(49]:** But these are responsible for contrst enhancement

**Commented [AC50R49]:** Yes they are but in this point we would to discuss the ability of gradient echo sequences in highlight susceptibility artifact that can represent also neovascularization rather than only hemorrhages

**Commented [IM51]:** These artifacts may have represented hemorrhagic foci since bite wounds were reported in the medical record of this dog?cat?

**Commented [AC52R51]:** Yes we have specified it in the text

**Commented [CF53]:** DWI/ADC sequences

human medicine[Kim 1998, Desprechin 1999, Chiang 2009] and one recent case report in a cat.[Nagendran 2021] In humans, atypical diffusion (e.g., restriction to diffusion in gliomas and abnormally increased diffusion in brain abscess) is reported in 5-21% of the cases, however it is a characteristic that has not yet been reported in the veterinary literature.[Reddy 2006, Reiche 2010, Hakymez 2005]

In humans, the "dual rim sign" in SWI is the most specific imaging feature to distinguish gliomas and abscesses.[Toh 2012] This sign is typically seen in pyogenic abscesses while it has never been reported in gliomas.[Toh 2012] In our population, only one patient of the glioma group had a SWI available, showing some intralesional foci/tubular susceptibility artifacts without evidence of "dual rim sign". The lack of visualization of "dual rim sign" in this patient agrees with what is reported in human medicine. Unfortunately, due to the retrospective nature of our study, a SWI sequence was not included in the MRI protocol of any patient of the abscess group. Future studies are needed to investigate the utility of SWI sequence in veterinary medicine.

The major limitation of this study is the use of different MRI equipment and protocols. Low-field MRI might have failed in detecting small lesions. The different planes in some studies between the immediate and the delayed postcontrast T1W sequences might have biased the effective progression of the central enhancement.

Another limitation is that, due to the retrospective and multicenter nature of the study over a long period, different histological classification systems were used from different veterinary pathologists with different backgrounds. For this reason, we decided not to make a distinction between high- and low-grade ring-enhancing gliomas.

In conclusion, even if several overlapping MRI features between ring-enhancing gliomas and brain abscesses do exist, some features can help to prioritize the MRI diagnosis. The presence of a homogeneous T1W or T2W signal intensity, a T2W or T2*W GE peripheral hypointense halo and an even enhancing capsule may indicate a brain abscess. The central progression of

the enhancement on delayed postcontrast T1W sequences is indicative of glial neoplasia. The addition of DWI and SWI sequences available on high-field MR scanners should be considered for assessment of intra-axial brain lesions which cannot be easily discriminated using standard MRI sequences.

**Commented [IM54]:** My suggestion: The addition of DWI and SWI sequences available on high-field MR scanners should be considered for assessment of intra-axial brain lesions.

**Commented [AC55R54]:** Thanks, we rephrased it.

334 REFERENCES

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Table 1: MRI features of ring-enhancing gliomas and brain abscesses.

| | | | Glioma (n = 16) | Abscess (n = 15) |
|---|---|---|---|---|
| **Signal homogeneity** | T1W | Homogeneous | 4/16 | 10/15 |
| | | Heterogeneous | 12/16 | 5/15 |
| | T2W | Homogeneous | 0/16 | 5/15 |
| | | Heterogeneous | 16/16 | 10/15 |
| **Signal intensity** | T1W | Hypointense | 11/16 | 14/15 |
| | | Isointense | 4/16 | 1/15 |
| | | Hyperintense | 1/16 | 0/15 |
| | T2W | Hypointense | 0/16 | 3/15 |
| | | Isointense | 0/16 | 1/15 |
| | | Hyperintense | 16/16 | 11/15 |
| **T2/T2*W GE peripheral hypointense halo** | Presence | | 1/16 | 9/15 |
| | Absence | | 15/16 | 6/15 |
| **T2 FLAIR intralesional attenuating component** | Presence | | 10/16 | 9/15 |
| | Absence | | 6/16 | 6/15 |
| **T2 FLAIR white matter perilesional edema** | Grade 0 | | 5/16 | 1/15 |
| | Grade 1 | | 3/16 | 1/15 |
| | Grade 2 | | 4/16 | 4/15 |
| | Grade 3 | | 4/16 | 9/15 |
| **Pattern of ring-enhancement** | Even | | 1/16 | 10/15 |
| | Uneven | | 15/16 | 5/15 |
| **Progressive central enhancement of delayed T1W post-contrast** | Presence | | 9/12 | 1/10 |
| | Absence | | 3/12 | 9/10 |
| **Susceptibility artifacts on T2*W GE/SWI** | Presence | | 4/13 | 1/9 |
| | Absence | | 9/13 | 8/9 |
| **Behavior on DWI/ADC** | Increased diffusion | | 6/6 | 0/1 |
| | Decreased diffusion | | 0/6 | 1/1 |
| **“Dual rim sign” on SWI** | Presence | | 0/1 | N/A |
| | Absence | | 1/1 | N/A |

345 Table 2: Comparison between MRI findings in ring-enhancing gliomas and brain abscesses.

| | Gliomas N=16 | Abscesses N=15 | Chi-square test | P | Relative risk | 95%CI |
|---|---|---|---|---|---|---|
| **T2W homogeneous lesion** | 0 | 5 | 4.13 | 0.042 | 2.6 | 1.6-4.23 |
| **T1W homogeneous lesion** | 4 | 10 | 3.87 | 0.049 | 2.4 | 1.08-5.45 |
| **T1W and T2W homogeneous lesion** | 0 | 3 | 1.62 | 0.202 | | |
| **Intensity of the lesion on T2W sequences** | | | 4.90 | 0.050 | | |
| - **hyper** | 1 | 0 | 0.001 | 0.974 | | |
| - **iso** | 4 | 1 | 0.81 | 0.369 | | |
| - **Hypo** | 11 | 14 | 1.63 | 0.202 | | |
| **T2 FLAIR attenuating component** | 10 | 9 | 0.05 | 0.821 | | |
| **T2 FLAIR perilesional edema** | | | 5.56 | 0.162 | | |
| - **grade 2-3** | 8 | 13 | 3.23 | 0.072 | | |
| - **grade 0-1** | 8 | 2 | 1.63 | 0.202 | | |
| **Peripheral T2 hypointense halo** | 1 | 9 | 7.92 | 0.005 | 3.15 | 1.55-6.39 |
| **Peripheral T2*W GE hypointense halo** | 1 | 5 | 3.97 | 0.046 | 3.33 | 1.33-8.37 |
| **Susceptibility artifacts on T2*W GE sequences** | 1 | 4 | 0.32 | 0.572 | | |
| ~~**Regular**~~ **Even profile of the capsule on T1W + C sequences** | 1 | 10 | 9.85 | 0.002 | 3.64 | 1.66-7.95 |
| **Central progression of the contrast medium on delayed T1W + C** | 9 | 1 | 6.86 | 0.009 | 0.13 | 0.02-0.88 |

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Figure 1: Transverse T2W image of a one-year-old, neutered male, American Staffordshire Terrier with left thalamic abscess. Note the peripheral hypointense halo (arrow) surrounding a homogeneous hyperintense center. There is a moderate mass effect on the third ventricle (arrowheads) along with moderate T2 hyperintense vasogenic edema surrounding the lesion.

Figure 2: Immediate post-contrast T1W transverse (A) and dorsal delayed post-contrast T1W (B) images of a 9-year-old, male neutered, DLH cat with a right temporo-parietal lobe abscess secondary to a bite wound with temporal myopathy (arrows). Despite the different acquisition planes the thickness of the abscess' capsule does not increase over time (white arrowheads). Immediate post-contrast T1W (C) and delayed post-contrast T1W (D) transverse images of a 9-year-old, female spayed, Labrador Retriever with left cerebellar ring-enhancing glioma. Note the conspicuous central progression (black arrowheads) of the enhancement on the delayed post-contrast sequence.

Figure 3: (A-C) 9-year-old, male neutered, DSH cat with right parietal lobe abscess secondary to a bite wound. A well-defined ring-enhancing lesion with hypointense center (arrow) is visible on the T1 post-contrast sequence (A); right temporal myopathy and a calvarial defect are also visible ~~(you may need to add some annotation on the image to show this)~~(dashed arrow). On the transverse DWI (B) the central portion of the abscess is strongly hyperintense (black asterisk) while it shows low values (white asterisk) on the ADC map (C), consistent with restriction to diffusion. (D-F) 5-year-old, male, French Bulldog with ring-enhancing glioma of the right fronto-parietal lobe. The T1W post-contrast sequence shows an ~~irregularly~~ unevenly marginated ring-enhancing glioma (arrowheads) (D). On the transverse DWI (E) the central portion of the lesion is hypointense (white §) while on the ADC map (F) it shows high signal (black §), consistent with increased diffusion.

Note the difference between the even enhancing capsule of the brain abscess (A) compared to the unevenly marginated ring-enhancing glioma (D).

376 Appendix 1: MRI scanners characteristics for each institution.

| Institution | MRI machine |
|---|---|
| **Veterinary Hospital "I Portoni Rossi", Anicura Italy** | 1.5T, Vantage Elan, Canon Medical Systems Europe B.V., Zoetermeer, the Netherlands<br>0.22, T MrJ, Paramed, Genua, Italy |
| **Royal Veterinary College** | 1.5 T, Philips Intera, Philips Medical System, Guildford, UK |
| **School of Veterinary Medicine, University of Glasgow** | University of Glasgow<br>1.5 T, Magnetom, Siemens, Camberley, UK<br>Glasgow Burgess<br>1.5 T, Gyroscan ACS NT, Philips Medical System, Eindhoven, The Netherlands |
| **Vetsuisse Faculty, University of Bern** | 1.0 T, Philips Panorama HFO, Philips Medical Systems, Best, The Netherlands<br>3.0 T, Achieva, Philips Healthcare, Best, the Netherlands |
| **Faculty of Veterinary Medicine, University of Montreal** | 1.5T, GE Signa EchoSpeed HD, GE Healthcare, Chicago, Illinois, USA |
| **Neurología Veterinaria** | 1.5T, Gyroscan Intera, Philips, Eindhoven, The Netherlands |
| **Veterinary Hospital "Gregorio VII"** | 0.33 T MrV, Paramed, Genua, Italy |

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