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Multiple peripherally “ring” enhancing lesions of the brain in a young man: A diagnostic dilemma

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ABSTRACT

Primary central nervous system (CNS) lymphomas are tumours localised only in the brain, spinal cord, and rarely, the eyes (i.e. involving only the CNS). These can be detected by imaging modalities, namely computed tomography (CT) and magnetic resonance imaging (MRI), in which they appear as lesions, most often with surrounding enhancement (i.e. peripherally-enhancing or ring-enhancing lesions). However, similar lesions can be seen in a variety of other conditions and differentiating these diagnoses by imaging alone is difficult. We report a case of primary CNS lymphoma in a 21-year old gentleman who was misdiagnosed as and treated for neurocysticercosis and brain tuberculomas due to misleading investigation results, in addition to the relative unlikelihood of CNS lymphoma in this patient compared to other similar individuals. Fortunately, appropriate management was initiated as soon as CNS lymphoma was confirmed by biopsy of the brain lesion, with good treatment response.

Keywords: Primary CNS lymphoma; Peripherally-enhancing lesions; Ring-enhancing lesions; Diagnostic dilemma; MRI

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BACKGROUND

Primary CNS lymphoma (PCNSL), is an uncommon form of non-Hodgkin's lymphoma (NHL) that is restricted to the central nervous system (CNS), involving only the brain, leptomeninges, spinal cord, cerebrospinal fluid (CSF), and/or eyes, with no other systemic involvement ^{1,2}. 90% of PCNSLs are diffuse large B-cell lymphomas ¹, and can occur in patients with or without immunosuppression ³.

Imaging modalities to investigate PCNSL include computed tomography (CT) and magnetic resonance imaging (MRI) scans. Typically, PCNSL lesions are detected in periventricular and superficial areas within the brain parenchyma ⁴. On CT scans, these lesions appear iso- or hyperdense; on T1-weighted MRI scans they appear hypo- or isointense; whereas on T2-weighted MRI images they appear iso- or hyperintense lesions ^{4,5}. Most of the CT and MRI lesions show moderate-to-marked contrast enhancement, mostly homogeneously enhancing lesions in patients without acquired immunodeficiency syndrome (AIDS), and peripherally-enhancing or ring-enhancing lesions in patients with AIDS ⁴. Oedema and mass effect may also be found on imaging ⁴⁻⁶.

However, these lesions on CT and MRI scans are not specific for PCNSL. Possibilities include other cerebral neoplasms namely glioblastomas ^{7,8}, as well as infective causes such as neurocysticercosis ⁹, brain tuberculomas ⁹, cerebral toxoplasmosis ¹⁰, cerebral abscess ¹¹⁻¹³, neurological Chagas disease (trypanosomiasis)¹⁴, cerebral actinomycosis¹⁵, coccidiomycosis ¹⁶ among others. Distinguishing these diagnoses by imaging alone is not easy, which is important given that the different conditions require different management protocols.

Since the chances of detecting peripherally- or ring-enhancing lesions are quite likely in clinical practice (due to its association with multiple diseases), it is important to realise the potential diagnostic dilemma they may cause.

Additionally, accurate and prompt diagnosis is essential to avoid unnecessary morbidity and mortality.

CASE PRESENTATION

We present a 21-year old gentleman of South Asian descent who came to the hospital after having a generalised tonic-clonic seizure, preceded by 2 days of headache and vomiting. There was no history of fever. The patient had a similar seizure episode 1 year prior, but he was not investigated. Other than being an ex-smoker and having previous alcohol consumption, there was no other significant medical history.

On admission, he recovered relatively well after a short period of post-ictal confusion, with full conscious level and no neurological deficits. Initial blood tests were unremarkable apart from slight leucocytosis of 14,000/ μ L (normal range: 4,000 – 10,000/ μ L), i.e. normal electrolytes, kidney and liver functions, inflammatory markers.

Initial computed tomography (CT) scan of the head revealed multiple peripherally-enhancing lesions with surrounding oedema, mass effect and midline shift of 3.5mm to the left side, as shown in Figure 1 (A & B). This prompted the initiation of phenytoin as an anti-epileptic, along with dexamethasone to treat the cerebral oedema. Neurosurgical evaluation did not require urgent intervention to be carried out at that moment. Magnetic resonance imaging (MRI) of the brain was done which re-illustrated the CT findings of multiple lesions with surrounding oedema, see Figure 2 (A & B).

Cerebrospinal fluid (CSF) studies showed a lymphocytic picture, with 53/ μ L (normal range: 0 – 5/ μ L) white blood cells (WBC), of which 98% consisted of lymphocytes. CSF glucose was normal, and protein was high at 0.82 g/L (normal range: 0.15 – 0.85 g/L). Epstein Barr virus (EBV) was positive in the CSF, with the polymerase chain reaction (PCR) test returning a value of over 1900 IU/mL. Other CSF studies were negative, namely Gram stain, bacterial and fungal culture, smear for acid-fast bacilli (AFB),

as well as PCR tests for tuberculosis (TB), adenovirus, cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus PCR,

mumps virus PCR, parechovirus PCR, and enterovirus PCR. Human immunodeficiency virus (HIV) screening was also negative.

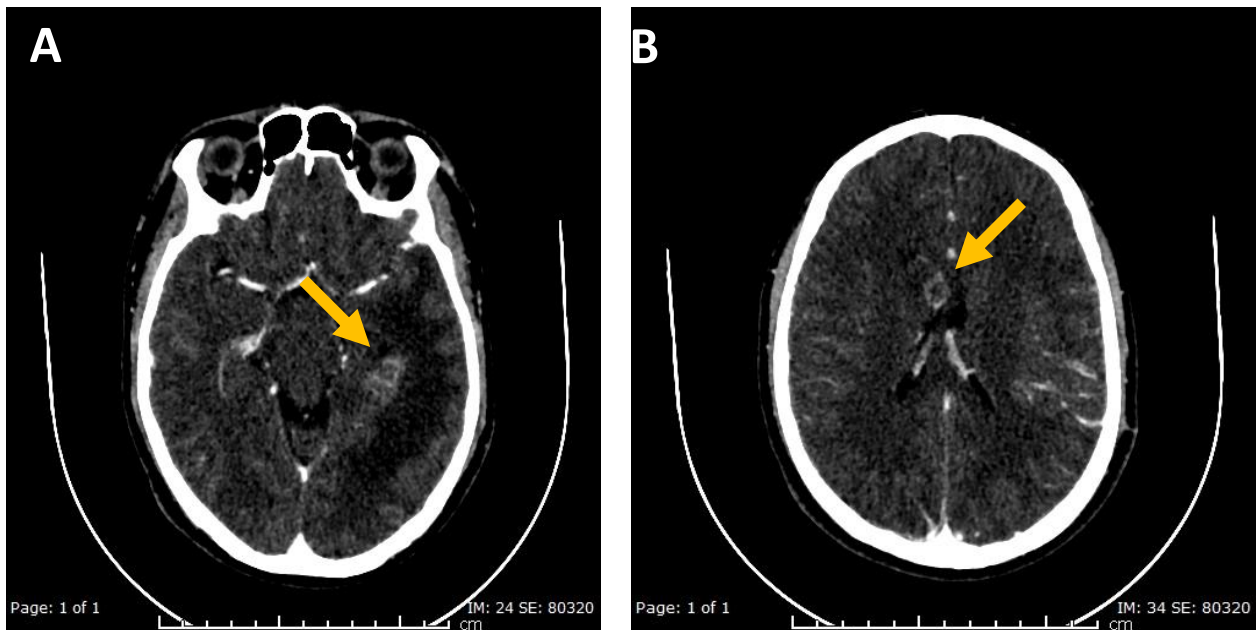


Figure 1: Axial CT scan of the brain with IV contrast administration, showing 2 ring-enhancing lesions. A: Ring-enhancing lesion in the left temporal lobe with surrounding perifocal oedema (yellow arrow in A). B: Another ring-enhancing lesion in the right periventricular region adjacent to right lateral ventricle with mild mass effect on the ventricle (yellow arrow in B).

At this point, considering the patient's history, demographics, and investigation results, a working diagnosis of either neurocysticercosis or brain tuberculomas was made. Empiric treatment was started, i.e. albendazole and anti-tuberculous medications, along with steroids. Anti-epileptic medications were changed to levetiracetam to avoid drug interactions. As the patient was clinically asymptomatic, he was discharged home on the previously mentioned medications.

2 weeks later, he arrived at the emergency department with 2 days of headache and vomiting, along with multiple fainting episodes, night sweats and weight loss (4 kg over 2 weeks). There was no history of fever or cough. Comparable to his previous presentation, initial neurological examination was unremarkable. As his symptoms did not improve, a repeat head CT scan was carried out, which showed worsening of the previous lesions, and increasing oedema,

with left-sided uncal herniation. A repeat brain MRI revealed a similar picture of the lesions, with increased enhancement and size, seen in Figure 2 (C & D).

Due to progression of disease whilst on anti-helminthic and anti-tuberculous management, other diagnoses had to be considered in this patient. Hence, MR Spectroscopy was done, which showed increased choline peak, decreased N-Acetyl Aspartate (NAA) peak, reversed choline/creatine ratio and high lipid/lactate peak. These findings are highly suggestive of lymphoma. Metastatic disease was a less likely possibility. As a staging CT scan of the thorax, abdomen and pelvis showed no suspicious deposits elsewhere, the patient was diagnosed with primary central nervous system (CNS) lymphoma.

After a multidisciplinary discussion, involving neurologists, neurosurgeons, and oncologists, it was decided to proceed with a brain biopsy,

which was carried out approximately 3 weeks from the second presentation. During the procedure, it was noticed that the patient had unequal non-reactive pupils shortly after induction of anaesthesia, which prompted the neurosurgical team to perform a decompressive craniectomy together with the stereotactic brain biopsy. The patient recovered from surgery well, with resolution of anisocoria and conscious level.

Histopathological examination of the brain lesion was consistent with a diagnosis of large B cell lymphoma (with a differential diagnosis of follicular lymphoma). Immunohistochemistry (IHC) studies were positive for CD45, CD20, CD79a, MUM-1, BOB-1, Bcl-2, Bcl-6, and negative for CD3, CD5, EBV, CD-10 and GFAP. Ki-67 index was 70% and C-MYC was positive (~40%). Flow cytometry was consistent with CD10-positive mature B-cell neoplasm.

Haematology team was involved, and a multidisciplinary meeting was held, during which a decision was made to proceed for urgent life-saving chemotherapy. Screening tests were unremarkable for HIV, hepatitis, syphilis, herpes simplex virus (HSV), cytomegalovirus (CMV), EBV, and toxoplasma. Full body fluorodeoxyglucose positron emission tomography (FDG PET) scan confirmed hypermetabolic foci in the brain, with no extracranial involvement. Bone marrow studies showed no lymphoma involvement.

Hence, the patient was started on the MATRix chemotherapy protocol (methotrexate, cytarabine, thiotepa, rituximab). Chemotherapy was well tolerated, with minimal side effects. No neurological deficits were noticed throughout the treatment period. The patient received 2 cycles of MATRix chemotherapy. He expressed his wishes to return to his home country and continue treatment there, with his family. Therefore, arrangements for travel were made, and patient underwent hypo-fractionated whole brain radiotherapy (30 Gy in 10 fractions, 3 Gy per fraction), which he tolerated well. MRI brain done after radiotherapy showed near complete

resolution of the previous PCNSL lesions, as in Figure 2 (F & G).

The following images show the sequence of MRI studies done on the patient throughout his illness and treatment course.

DISCUSSION

It can be seen in this case that primary CNS lymphoma is a diagnosis that may be missed, especially in a group of patients who, more often than not, have neurocysticercosis or brain tuberculomas, and present to the hospital in a similar manner. Moreover, initial imaging could reveal almost identical findings, which may not help in establishing the correct diagnosis, as can be seen below (Figure 3 to Figure 9).

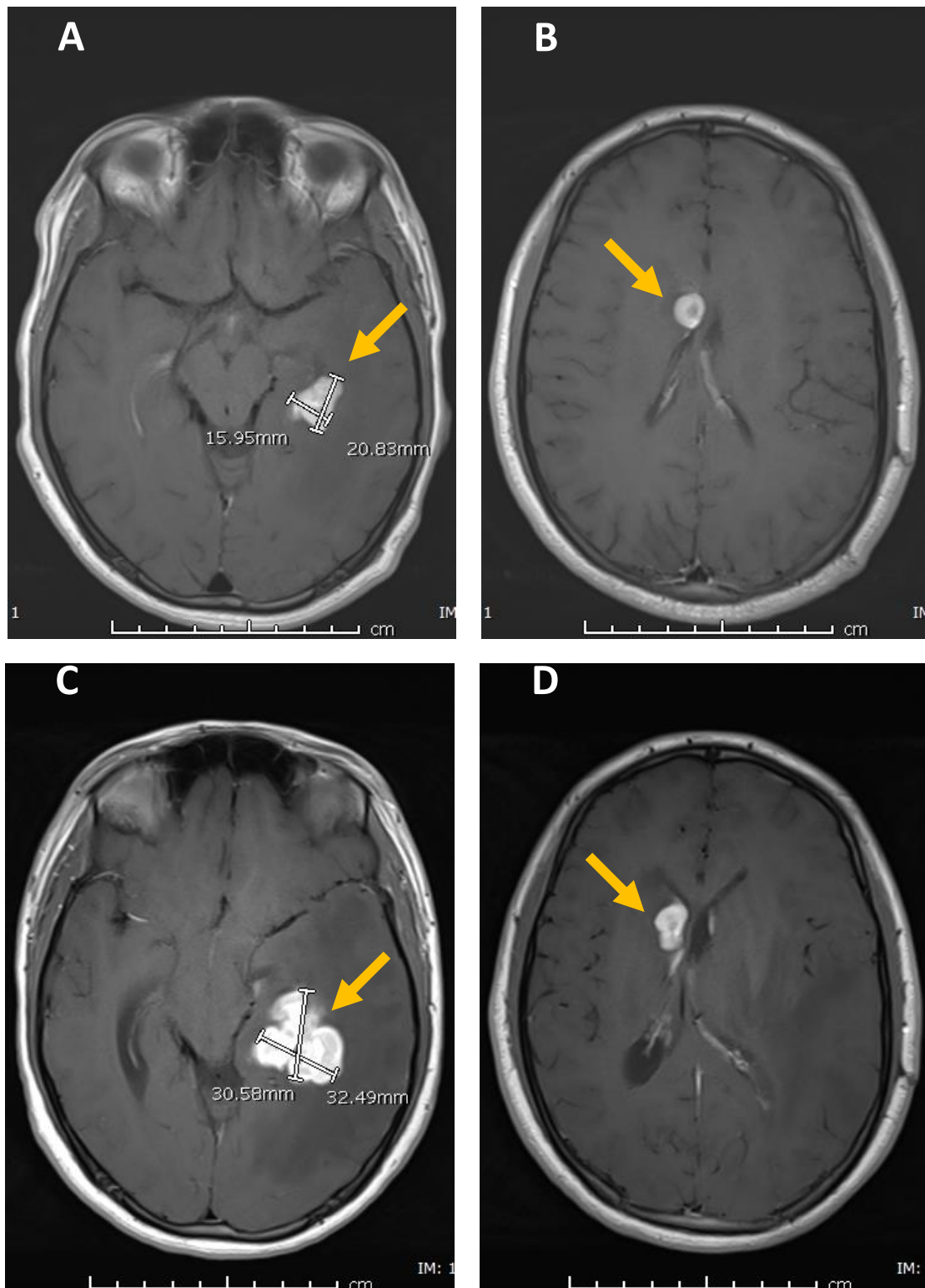
The similar appearances of peripheral- or ring-enhancing lesions in different conditions has been previously reported, especially in differentiating between neurocysticercosis and brain tuberculomas^{9,16,17}. This diagnostic dilemma is made worse by the fact that less invasive tests cannot really exclude neurocysticercosis or brain tuberculomas. For example, there are no blood/CSF analyses that can exclude these diagnoses. A simple Mantoux test, or interferon-gamma (IFN- γ) release assays (IGRA), or even polymerase-chain reaction (PCR) tests for tuberculosis may be negative in certain tuberculous infections, including tuberculomas of the brain. Serological tests for neurocysticercosis, including enzyme-linked immunosorbent assay (ELISA) and electroimmunotransfer blot (EITB), are also not 100% sensitive¹⁸. Only a histopathological analysis can provide diagnostic certainty.

It is worth noting that MR spectroscopy may provide insights to these brain lesions, and help distinguish the differential diagnoses to a certain extent. For example, most brain tumours show decreased N-acetyl aspartate (NAA) signals, increased choline (Cho), and hence increased Cho/NAA ratios¹⁹. Areas of ischaemia or infarction are likely to show increased lactate (due to anaerobic glycolysis), whereas gliomas show increased *myo*-inositol (ml) levels¹⁹.

Tuberculomas are associated with a lipid peak and decreased NAA²⁰. In addition, TB lesions mostly show a singlet peak ~3.8ppm, which are not found in most malignancies²¹. On the other hand, high Cho/creatine (Cr) and ml/Cr ratios point towards malignancies rather than tuberculomas²¹. Neurocysticercosis lesions show a combination of increased lactate,

alanine, succinate, Cho, but decreased NAA and Cr²⁰.

Nevertheless, final diagnosis will require biopsy of the lesion. Other tests may be useful guides, as a confirmatory biopsy is an invasive procedure with its own risks.



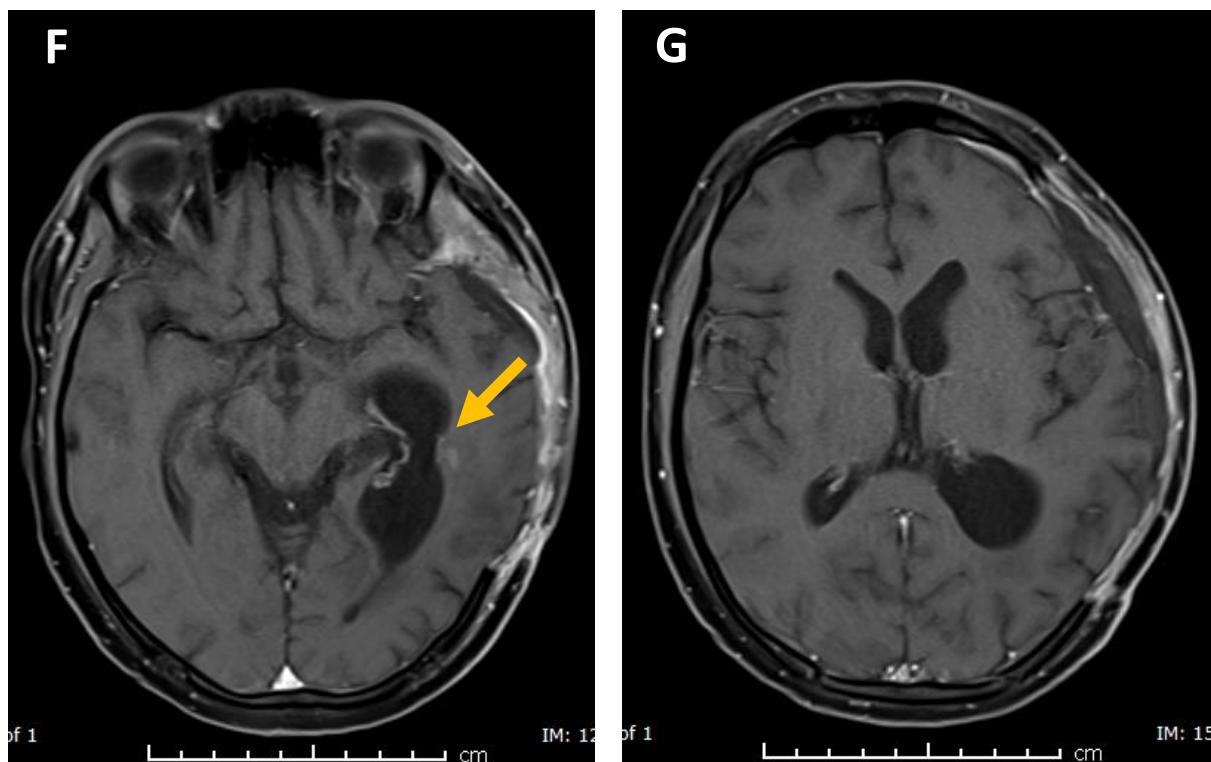
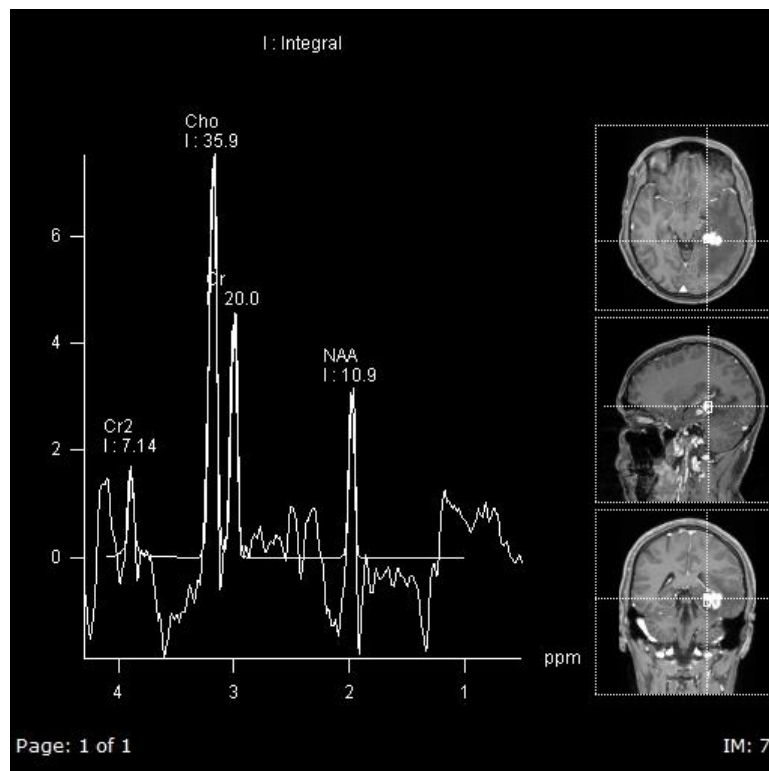


Figure 2 (A through F): MRI (axial T1-weighted post-contrast) images of the brain.

A&B: At initial diagnosis showing 2 ring-enhancing lesions (the first in the right caudate lobe and the second in the left temporal lobe) with mild perifocal oedema (yellow arrows). C&D: Follow-up image after 2 weeks showing increase in size of the lesions as well as surrounding perifocal oedema (yellow arrows). E: MR spectroscopy showing increased choline peak, decreased N-Acetyl Aspartate (NAA) peak, reversed choline/creatine ratio and high lipid/lactate peak, which is highly suggestive of lymphoma. F&G: Post-biopsy and treatment showing post-operative changes (left temporal craniotomy & small extra axial fluid) and almost complete clearance of the previously described lesions (only small residual enhancing focus still seen in the left temporal lobe) (yellow arrow).



Figure 3:Neurocysticercosis. Case courtesy of A.Prof Frank Gaillard, Ra-diopaedia.org, rID: 4772.

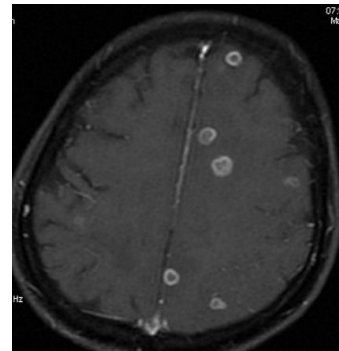


Figure 4:Tuberculomas. Case courtesy of Dr Sachin Pathak, Radiopaedia.org, rID: 13061.

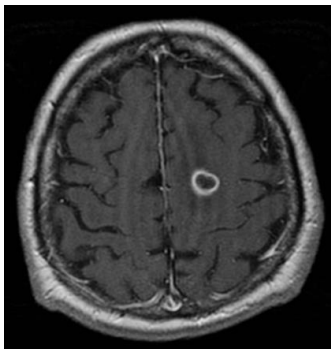


Figure 5:Cerebral abscess. Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 4933.



Figure 6:Glioblastoma multiforme.Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 4756.

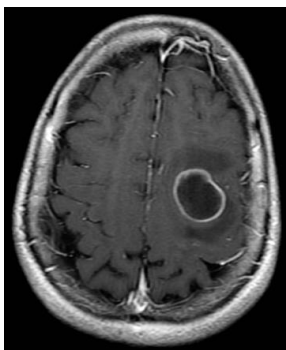


Figure 7: Cerebral metastasis. Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 5563.

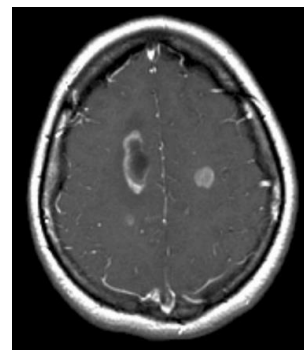


Figure 8: Acute disseminated encephalomyelitis. Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 2576.



Figure 9:Subacute haemorrhagic stroke.Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 4978.

CONCLUSION

It may not be feasible to subject all patients with brain lesions on CT or MRI to a brain biopsy. The benefits of establishing a diagnosis may not outweigh the risks of such an invasive procedure. It is also not cost effective for such an invasive procedure to be carried out on a large number of patients, with high rates of false negative results. On the other hand, missing a CNS lymphoma, or a delaying appropriate treatment can lead to dire, if not fatal, consequences. Therefore, patients treated empirically should be followed up, and those not responding or progressing on empiric therapy (e.g. anti-helminthic or anti-tuberculous treatment), other diagnoses should be considered (e.g. PCNSL).

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