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Clinical Reasoning: A 73-year-old man with recurrent aphasia, headaches and confusion

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**Section 1.**

A 73-year-old man presented with sudden right-sided weakness, aphasia, and low-grade headache. Medical history was pertinent for obstructive sleep apnea, hypertension, diabetes, and dyslipidemia, for which he was appropriately treated, in addition to taking aspirin for primary prevention. Initial blood work, head CT, and vessel imaging were normal. Magnetic resonance imaging (MRI) showed a non-enhancing, non-restricting, T2 hyperintensity in the left temporal lobe, in addition to multiple microhemorrhages (Fig.1a-b). Symptoms resolved within 24 hours and he was discharged on a second antiplatelet agent, clopidogrel. Three weeks later, a second episode of aphasia and right-sided weakness occurred, resolving within hours. He returned to hospital the following day as symptoms recurred again. He had had been continually complaining of headaches, and his family had noted a gradual cognitive decline over the past month. Repeat blood work and ESR was normal. MRI demonstrated persistent microhemorrhages and superficial siderosis, worsening of the left temporal lobe subcortical changes, as well as diffuse leptomeningeal enhancement.

**Questions for consideration:**

1. What is the differential diagnosis for recurrent neurologic symptoms?
2. What investigations ought to be considered given this differential and MRI findings?

**Section 2.**

The differential included transient ischemic attack, although lack of diffusion restriction on MRI and stereotyped events despite normal vessel imaging made this less likely. An

echocardiogram and 72-hour Holter monitor were done and also normal. Recurrent events are typical of focal seizures, and given the increasing temporal lobe hyperintensity, a low-grade glioma was a potential cause and levetiracetam was initiated. A routine 1-hour electroencephalogram (EEG) was performed and did not capture any clinical events or epileptic abnormalities; however, the medication was continued. The patient's age, headaches, and focal neurologic symptoms prompted investigation for giant-cell arteritis, though erythrocyte sedimentation rate were normal.

The leptomeningeal enhancement was investigated with cerebrospinal fluid (CSF) analysis, which showed marked elevation in protein at 1.87g/L; however, there were zero total nucleated or red blood cells/microlitre, the gram stain was negative, normal CSF glucose, no detected oligoclonal bands were detected, and flow cytometry and cytology testing were negative for malignancy. No opening pressure was obtained. Given the absence of total nucleated cells, and lack of fever, herpes simplex virus was not sent despite the temporal lobe abnormality on MRI. The elevated protein was suggestive of an inflammatory etiology, yet vessel imaging did not show changes suspected for primary angiitis of the CNS (PACNS), and a CT chest was performed that did not show hilar lymphadenopathy that can be seen in sarcoidosis. Despite a negative CSF cytology and flow cytometry, lymphoma was still a potential differential and a CT abdomen and pelvis was performed without abnormality.

The clinical course of recurrent neurologic symptoms, headache, and cognitive decline, presence of multiple microhemorrhages with superficial siderosis and leptomeningeal

enhancement, and inflammatory CSF analysis was suggestive of amyloid-beta related angiitis (ABRA).

**Questions for consideration:**

1. What further investigations would assist in the diagnostic clarification for this patient?
2. What is the definition and treatment of ABRA?

**Section 3.**

Treatment for the presumed diagnosis of ABRA was initiated with a 5-day course of intravenous methylprednisolone 1000mg daily followed by oral prednisone 50mg per day, and clopidogrel was discontinued. Brain biopsy and cyclophosphamide were recommended, however the headaches, neurologic examination and leptomeningeal enhancement improved. Consequently, the patient and his family deferred brain biopsy with sampling of parenchyma and meninges, the gold standard test for ABRA. The patient's cognitive testing initially improved from a Montreal Cognitive Assessment (MoCA) of 20/30 to 24/30 after one month of therapy, however he remained fatigued, attributed to steroid use and weaned to 40mg daily one month post-discharge. Two months post-discharge, methotrexate was added to prednisone to reduce risk of ABRA recurrence. Despite these adjustments, the patient's fatigue worsened and his cognition progressively declined.

Six months post-discharge, the confusion had progressed, headaches worsened, and the patient developed gait difficulty prompting return to hospital. Blood work including

absolute neutrophil count, thyroid, liver and renal function, serum inflammatory markers including ESR, antinuclear antibody (ANA), and antineutrophil cytoplasmic antibody (ANCA) were normal. An infectious work-up for HIV, syphilis, and Lyme borreliosis was negative. Repeat CSF analysis yielded protein elevation at 1.06g/L, slightly less than previous, and again zero total nucleated cells or red blood cells were detected, cytology was negative, CSF glucose was normal, and gram stain, fungal culture, and mycobacterium culture were negative, and again opening CSF pressure was not obtained. Creutzfeldt-Jakob disease testing with CSF 14-3-3, tau, and Endpoint Quaking-induced Conversion (EP-QuiC) assay were negative. Both serum and CSF paraneoplastic and autoimmune antibody panels were negative. Repeat CT chest, abdomen, and pelvis were negative. MRI showed resolution of the previously observed left temporal hyperintensity, but development of a new left parietal infarct with petechial hemorrhages, as well as worsening leptomeningeal enhancement (Fig.1c).

**Questions for consideration:**

1. What could be the reason for the patient's worsening?
2. Are there any further tests that would be helpful in this patient's case?

**Section 4.**

Due to concern for ABRA recurrence, a course of intravenous immunoglobulin G (IVIG) 2g/kg over 5 days followed by intravenous methylprednisolone 1000mg daily for 5 days was delivered. Brain biopsy and cyclophosphamide were again recommended; however, as the patient's cognitive status and expected quality of life were guarded, after

discussion with the family no further diagnostic investigations or treatments were pursued. The patient passed away and subsequent autopsy was performed.

Neuropathological examination revealed significantly thickened arachnoid and a 4x2.5x3.5cm subacute left parietal infarct. At microscopy throughout the cerebral hemispheres amyloid beta accumulation was found within intracortical and arachnoidal artery and arteriole walls, at times fragmented (Fig.2a), and focally surrounded by mononuclear inflammatory cells. Focal hemosiderin was noted in the arachnoid. In addition to this first process the arachnoid was filled with granulomas (Fig.2b) with halo-surrounded budding organisms in keeping with *Cryptococcus sp.* yeast (Fig.2c). The arachnoid near to the infarct was especially involved, and the arteries showed obliterating endarteritis, likely causing the infarct.

#### **Questions for consideration:**

1. What are the risk factors for developing cryptococcal meningoencephalitis?
2. What is the diagnostic yield of CSF culture for *Cryptococcus sp.* yeast and what is the most specific and sensitive test?
3. What is the treatment for cryptococcal meningoencephalitis? What is the prognosis?

#### **Discussion**

*Cryptococcus neoformans* is a yeast responsible for 30–66 infections in the United States annually and is the most common fungal infection of the CNS world-wide (CNS).(1) In HIV patients with CD4 count less than 100 cells/microlitre in the United States, incidence

of cryptococcal meningoencephalitis may be as high as 3%.(2) In HIV-negative patients who are immunocompromised, as in our patient, there may not be signs of raised intracranial pressure (ICP) or disseminated fungemia. CSF analysis may show increased opening pressure, elevated total nucleated cell counts of 20 to 200 cells/microlitre of predominantly monocytes, and hypoglycorrhachia, which was not the case in our patient, although elevated CSF protein is also reported.(3) Gram stain is typically normal with *Cryptococcus neoformans* due to resemblance to host lymphocytes, and fungal culture is often normal. However, cryptococcal antigen in CSF can be detected quickly with either latex agglutination test assays or enzyme-linked immunoassays that both yield sensitivities and specificities over 90%, and has been reported to be present 3 weeks prior to neurologic symptoms.(4) Treatment of cryptococcal meningoencephalitis requires antifungals, control of raised ICP, and reducing immune suppression. Induction with intravenous amphotericin B plus oral flucytosine for at least six weeks in patients with neurologic involvement, followed by oral fluconazole for an additional eight weeks is recommended.(5) The prognosis is dependent on underlying comorbidity and cryptococcal antigen titres, but even with prompt adequate treatment, mortality may be 10-30%.(6)

Patients may have non-specific symptoms, such as headaches, cognitive changes, and ataxia, with either cryptococcal meningoencephalitis or ABRA. Furthermore, CSF analysis in ABRA can also show increased opening pressure, elevated protein and total nucleated cells. MRI may not differentiate ABRA from cryptococcal meningoencephalitis, as both may show leptomeningeal enhancement, cerebral atrophy



or hydrocephalus, and occasionally cerebral infarcts, as in our patient.(7) Clinical and radiographic findings can have high likelihood of detecting ABRA, however require absence of neoplastic, infectious or other cause.(8) Thus, biopsy of brain parenchyma or meninges with examination of vasculature is needed for definitive diagnosis. Tissue biopsy in ABRA will show amyloid beta accumulation within the regions of vasculitic vessel wall destruction, as was seen in our patient on autopsy, and differentiates from PACNS, sarcoidosis, or intravascular lymphoma. Initiation of immune suppressive medication improves outcomes in ABRA, as seen initially for our patient's clinical symptoms, cognitive testing, reduced CSF protein, and resolution of the left temporal lobe lesion.(9) Although, the subsequent immunocompromised state can leave a patient susceptible to opportunistic infections, which may have been the sequence of events resulting in cryptococcal meningoencephalitis in our patient.

A high index of suspicion for cryptococcal meningoencephalitis in patients on immune suppression with nonspecific symptoms, and testing CSF cryptococcal antigen, is important as this is a potentially treatable entity with high mortality.

**Appendix 1: Authors**

<b>Name</b>	<b>Location</b>	<b>Contribution</b>
Gauruv Bose, MD	The Ottawa Hospital, University of Ottawa	Collected and synthesized the data; drafted the manuscript for intellectual content.
Tess Fitzpatrick, MD	The Ottawa Hospital, University of Ottawa	Collected and synthesized the data; drafted the manuscript for intellectual content.
Vignan Yogendrakumar, MD	The Ottawa Hospital, University of Ottawa	Revised the manuscript for intellectual content.
Jocelyn C. Zwicker, MD	The Ottawa Hospital, University of Ottawa	Revised the manuscript for intellectual content.
Gerard H. Jansen, MD	The Ottawa Hospital, University of Ottawa	Collected and synthesized the data; drafted the manuscript for intellectual content.

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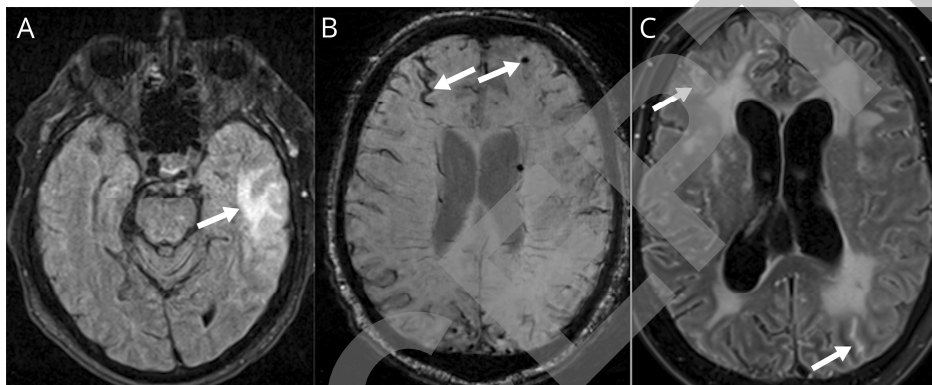
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**Figure Legends****Figure 1. Magnetic resonance imaging characteristic of amyloid beta-related angiitis**

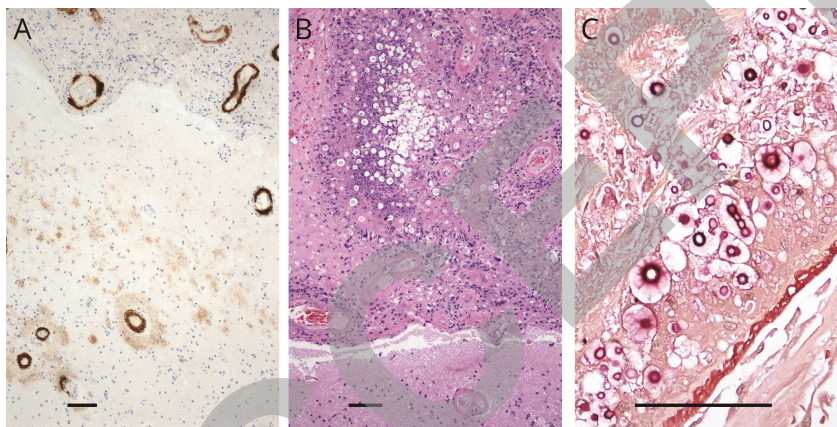
(A) T2 fluid attenuated inversion recovery image showing left temporal lobe hyperintensity (arrow). (B) Susceptibility weighted images showing microhemorrhages and superficial siderosis (arrows). (C) Six-month gadolinium-enhanced T2 fluid attenuated inversion recovery showing leptomeningeal enhancement (arrows).



**Figure 2. Microscopical examination post-mortem demonstrating findings of amyloid beta-related angiitis and cryptococcal meningoencephalitis**

(A) Amyloid beta antibody staining showing amyloid beta accumulation within cortical arterioles, occasionally with irregular interruptions due to previous amyloid phagocytosis.

(B) Granulomatous inflammation of arachnoid (hematoxylin and eosin). (C) Arachnoid with mucin carmine showing *Cryptococcus* species organisms. Size bar indicates 100  $\mu\text{m}$ .



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