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Case study

Clinical pathologic case report: A 70-year-old man with inflammatory cerebral amyloid angiopathy causing headache, cognitive impairment, and aphasia

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1. Case description

A 70-year-old man with diabetes mellitus, hypertension, and hyperlipidemia was in his usual state of health when he developed generalized malaise for one week followed by left retro-orbital headache with associated nausea and vomiting. He attended urgent care and was treated with intravenous analgesics with relief. A week later, he noticed word-finding difficulties, leftsided vision loss and inability to function at his job. He presented to a hospital, where a computed tomographic (CT) scan of his head was normal, and he was discharged home. Two days later, he represented and was admitted with new onset speech arrest and visual hallucinations. He had no history of fevers. Brain magnetic resonance imaging (MRI) was reportedly abnormal, but this was not thought to fully explain his clinical decline. He had an extensive evaluation, and was diagnosed with a viral meningoencephalitis and treated with IV acyclovir until the CSF HSV PCR returned negative. Over the course of two weeks his clinical status improved. He was discharged to a rehabilitation facility. One week

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ABSTRACT

A 70-year-old man presented with two months of worsening cognitive impairment, hallucinations, and difficulty speaking, with superimposed headaches. Cerebrospinal fluid analysis was notable for lymphocytic pleocytosis and elevated protein. Imaging studies revealed multiple acute and subacute infarcts with cortical microhemorrhages. The patient underwent a stereotactic brain biopsy. In this article, we discuss the patient's differential diagnosis, pathologic findings, ultimate diagnosis, and clinical outcome. © 2017 Published by Elsevier Ltd.

> later, he was readmitted after a fall with head strike in the setting of ongoing agitation and hallucinations. Repeat Brain MRI and lumbar puncture were again abnormal. He was transferred to our hospital for further evaluation and management.

> On admission to our hospital his neurologic examination was abnormal. He intermittently picked at the air. He had a paucity of speech and impaired word retrieval. He was oriented to year, but not to month or hospital. He perseverated and was inattentive. His long-term memory was intact when speaking about his prior employment. Visual fields and extraocular movements were intact but optic ataxia was present. Tone, power, and reflexes were normal bilaterally. Plantar reflexes were flexor.

> Throughout his hospitalization, his neurological and mental status examinations waxed and waned. At his best, he was attentive, fully oriented and demonstrated moderate insight into his care and treatment plan. Episodically, he experienced acute agitation, hallucinations, expressive aphasia, and right-sided facial weakness that resolved within hours.

2. Results

Laboratory testing of electrolytes, complete blood count, renal function and liver function was normal. The following serum studies were also negative or normal: thyroid-stimulating hormone,

ammonia, vitamin B12, C-reactive protein, erythrocyte sedimentation rate, thyroid peroxidase antibodies, human immunodeficiency virus antibodies, lyme enzyme-linked immunosorbent assay, rapid plasma reagin, antinuclear antibody, anti-neutrophil cytoplasmic antibody (ANCA), lupus anticoagulant, cryoglobulins. The following antibodies were negative or normal: Anti-smooth muscle, Antismith, double-stranded DNA, anti-Ro, anti-La, Beta-2 glycoprotein IgG and IgM, ribonucleoprotein (RNP), myeloperoxidase (MPO), proteinase 3 (PR-3). Complement C3 was normal at 132 mg/dl. C4 was mildly elevated at 44 mg/dl. Serum and urine protein electrophoresis were normal.

Three lumbar punctures were performed during his hospitalizations and are reported in Table 1. All were inflammatory with a lymphocytic predominance. CSF was negative for herpes simplex virus (HSV) 1 and 2 on serial studies as well as at least one negative result for Eastern equine encephalitis virus (EEE) IgM, Powassan virus IgM, West Nile virus (WNV) IgM and IgG, Cryptococcus antigen, and Treponemal IgG antibody. CSF bacterial culture grew no organisms. CSF flow cytometry revealed 90% of the cells were CD3-positive T cells (CD4:CD8 ratio of 4.1). CSF cytology showed an increased number of lymphocytes, including occasional reactive forms.

Serum and cerebrospinal fluid (CSF) paraneoplastic panels were negative. CSF neuron-specific enolase and 14-3-3 protein were negative.

The patient's brain MRI on repeat admission to the outside hospital is shown in Fig. 1 and notable for bilateral deep white matter hyperintensities consistent with small vessel disease as well as restricted diffusion in the left parietal lobe. A follow-up MRI ten days later at our institution is depicted in Fig. 2 and demonstrates new areas of restricted diffusion in bilateral hemispheres. Additionally, multiple susceptibility-weighted imaging (SWI) lesions suggestive of cortical microhemorrhages were found. These micro-

Table 1

Laboratory data - Lumbar puncture results.

hemorrhages were not seen on outside imaging which used gradient echo sequence rather than SWI. Findings from CT and repeat MRI studies also revealed a new left subdural hematoma (SDH) with associated mild midline shift. Of note, this was after the fall sustained at the rehabilitation facility. CT and MR angiogram of neck and head showed no evidence of a vasculopathy, dural arteriovenous fistula or cortical venous sinus thrombosis.

Initial electroencephalogram (EEG) performed on day 9 at the outside hospital demonstrated diffuse encephalopathy with intermittent frontotemporal rhythmic slowing. EEGs performed following discovery of left SDH at our hospital revealed occasional left temporal focal delta slowing and bilateral semi-rhythmic slow waves consistent with left temporal cerebral dysfunction and bihemispheric encephalopathy. No epileptiform discharges or electrographic seizures were seen. We did not capture any acute episodes of agitation, aphasia or right facial weakness while on EEG.

Transthoracic echocardiogram (TTE) was normal. Transesophageal echogram (TEE) was aborted due to inability to traverse the esophagus. Transcranial doppler High-Intensity Transient signals (HITs) were negative for cerebral emboli. CT examination of the chest, abdomen, and pelvis revealed no evidence of malignancy.

3. Discussion

This patient's rapid evolution from highly functional to markedly cognitively impaired over a course of two months focuses the differential diagnosis on a rapidly progressive dementia (RPD). The inflammatory CSF and abnormal brain imaging suggest infectious, inflammatory, or vascular etiologies as most likely, but also possible are autoimmune, neoplastic, prion disease, and nonprion neurodegenerative etiologies. According to data from 1160

Variable	Reference range	Hospital Day 9	Hospital Day 24	Hospital Day 33	
Total nucleated cells (/µL)	0.00-0.02	62	24	1	
Neutrophils (%)	-	-	4.0	11	
Lymphocytes (%)	-	-	80.0	54	
Monocytes/Macrophages (%)	-	-	16.0	26	
RBC Count (/µL)	-	28	1600	42	
Xanthochromia	Negative	NA	Negative	Present	
Total Protein (mg/dl)	10-44	221	113	62.9	
Glucose (mg/dl)	40-70	49	50	137	



Fig. 1. Brain MRI, axial cuts. Images obtained hospital day 24 from initial hospitalization. (A) Diffusion-weighted imaging (DWI) and (B) apparent diffusion coefficient (ADC) sequences show small area of restricted diffusion in left parietal lobe. (C) Fluid attenuated inversion recovery (FLAIR) sequence demonstrates T2 hyperintensities in deep white matter. (D) Gradient echo sequence is without evidence of microhemorrhages.

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Fig. 2. Brain MRI, axial cuts. Images obtained hospital day 34 from initial hospitalization. (A) DWI and (B) ADC sequences show areas of restricted diffusion in bilateral hemispheres. (C) FLAIR sequence again demonstrates T2 hyperintensities in the deep white matter along with a new left SDH. (D) SWI sequence reveals cortical microhemorrhages.

autopsies over a 10-year period 23% of cases of RPD had "treatable causes" [1]. A systematic and comprehensive evaluation was therefore appropriately undertaken in efforts to identify a reversible etiology.

Although the time course in this case is not typical, non-prion neurodegenerative disease is a possible etiology in patients with RPD. Studies have shown that non-prion neurodegenerative explanations for RPD were found in 36.8% of subjects [2]. Additionally, non-prion neurodegenerative diseases are overall the most common cause of cognitive decline in older individuals. In this patient's case, however, collateral history from the patient's partner confirmed an acute change. Further, neurodegenerative conditions such as Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD) and dementia with Lewy body disease (DLB) would not explain his CSF or imaging findings.

Prion disease should be considered in any case of RPD. Typical signs of prion disease include myoclonus, 1–2 Hz epileptiform discharges [3], and brain MRI with hyperintensity and restricted diffusion in the cortical gyri and basal ganglia [4]. Our patient lacked these typical findings. Additionally, CSF 14-3-3 protein was negative, although this is an imperfect test that lacks the sensitivity and specificity needed to dramatically alter pre-test probability of having CJD [3]. Lastly, the CSF pleocytosis seen in this patient would be uncommon in prion disease [5].

The patient's abnormal CSF, rapid clinical progression, and ischemic/hemorrhagic brain lesions could be explained by an autoimmune or paraneoplastic cause. Autoimmune encephalitis often presents with early limbic involvement and patients may present with memory and/or behavioral disturbances. CT examination of chest, abdomen and pelvis was negative for malignancy. The normal serum and CSF paraneoplastic panels made a known syndrome less likely but did not entirely exclude the possibility of an autoimmune condition for which the antibody has not yet been identified. The ischemic and hemorrhagic brain lesions could represent emboli from marantic endocarditis which is sometimes seen in the context of autoimmune conditions and malignancy. Serum markers for an autoimmune condition were uniformly negative. TTE exonerated a large vegetation on a cardiac valve, but unfortunately the more sensitive transesophageal echo was not obtained due to patient factors [6].

Infection is a distinct possibility in the presence of such an inflammatory CSF profile. The time course for this patient, as well as only moderately elevated white blood cells with a lymphocytic pleocytosis, argues against bacterial meningoencephalitis. Elevated protein and normal glucose are seen in viral infections but again, the prolonged time course and negative CSF viral studies argue against this. HSV PCR can be falsely negative, particularly early in the illness [7] but in this patient's case, multiple lumbar punctures were obtained with serial negative HSV PCRs. Blood and CSF additionally failed to grow any organisms. The CSF profile is not consistent with a fungal or tubercular etiology given normal CSF glucose. Serum TB and lyme tests were both negative. In absence of culture growth, it is also less likely that the ischemic and hemorrhagic brain lesions represent septic emboli, although echocardiography was obtained as discussed.

The presence of multifocal areas of diffusion restriction as well as microhemorrhages raises particular concern for a vascular process - likely an inflammatory one given the composition of the CSF. Reversible cerebral vasoconstriction syndrome (RCVS) is a consideration given his initial headache although his headache lacked the 'thunderclap' quality. RCVS also typically affects younger people, aged 20–40 years and women more than men. However, CSF is often normal [8], which differed from this patient's case. Primary and secondary vasculitides could explain both imaging and CSF findings. Secondary vasculitis is less likely in absence of a systemic autoimmune condition, of which there were no signs and symptoms for this patient. Primary angiitis of the central nervous system (PACNS), albeit extremely rare, accounting for just 1% of the systemic vasculitides [8], was a distinct possibility in this case. Angiography can be utilized to detect segmental narrowing in multiple vessels. In this case, neither CT nor MR angiography demonstrated any evidence of a vasculopathy. Although conventional angiography is often recommended in the evaluation of PACNS, this study was not completed as a positive or negative finding would not have confirmed or excluded PACNS. Brain biopsy remains the gold standard for diagnosis of this condition and was ultimately pursued [8].

Intravascular lymphoma is another inflammatory vascular process that can present with cognitive changes. Arguing against this process are the patient's lack of constitutional symptoms and absence of any skin changes. Additionally, CSF cytology and flow cytometry were unrevealing for lymphoma – although they are often falsely negative. Sensitivity of cytology and cytometry increases with additional samples [9] but it is often impractical to wait for the results of these serial studies. Brain biopsy is often the preferred method of diagnosis.

Non-inflammatory CAA results from deposition of beta-amyloid peptide within small to medium sized blood vessels of the brain and leptomeninges [10]. It may be asymptomatic and often discovered incidentally on brain imaging when strictly cortical microhemorrhages are seen on GRE or SWI sequences of MRI, distinguished from microhemorrhages strictly in deep grey structures, which

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suggest a hypertensive etiology. In this patient CAA alone could explain the microhemorrhages and silent strokes [11] but would not account for his inflammatory CSF or cognitive decline. There is however a subset of CAA, termed *inflammatory* CAA (iCAA), which is characterized by acute or subacute cognitive decline. Although CSF analysis may be normal, 50% of cases demonstrate lymphocytic pleocytosis with a WBC count greater than 5 cells/µl [12].

The most likely cause of this patient's symptoms and imaging findings is an inflammatory vascular process. Primary angiitis of the central nervous system and iCAA are more likely than intravascular lymphoma. In absence of a less invasive test to differentiate between these possibilities, and potential for change in management, a brain biopsy was obtained. Brain biopsies, in cases of rapidly deteriorating neurological conditions or dementia, have reported sensitivities in the range of 20–65% [9].

4. Pathologic discussion

The patient underwent a right craniotomy with biopsy of the dura and brain (Fig. 3). The dura specimen showed only mild reactive changes. A scout section of the right frontal brain was treated with formic acid and showed no evidence of prion disease. The remainder of the specimen was routinely processed and showed thickened small and medium-sized blood vessels positive for amyloid deposition and associated with a perivascular chronic inflammatory-cell infiltrate consisting predominantly of T-cells and macrophages. The final pathologic diagnosis was cerebral amyloid angiopathy with inflammation primarily involving leptomeninges (Fig. 3).

5. Clinical outcome

The patient was diagnosed with inflammatory CAA (iCAA) and started on pulsed high-dose steroid therapy with methylprednisolone 1 g daily for five days without improvement in his symptoms. He was subsequently started on cyclophosphamide infusion 15 mg/kg for six monthly cycles. Initially, he improved and was able to socialize with friends and return to work. His cognitive assessment, using the Montreal Cognitive Assessment (MoCA) increased from 21 to 24. Between his penultimate and last cyclophosphamide infusion, he began to have worsening memory problems and his MOCA dropped from 24 to 19. He was transitioned to mycophenolate mofetil, with stabilization of his symptoms.

6. Conclusions

CAA is age-dependent, affecting 2.3% of people between the ages of 65 and 74 and 12.1% over the age of 85 [13]. CAA refers to the deposition of beta-amyloid peptide in the media and adventitia of small- and medium-sized arteries and veins of the cerebral cortex and the leptomeninges [10]. Patients with CAA often present with spontaneous lobar intraparenchymal hemorrhages (IPH) and cognitive impairment but many other clinical manifestations are possible: IPH, subarachnoid hemorrhages, ischemic infarcts, focal seizures, transient ischemic attacks, cortical spreading depression phenomena or "amyloid spells," cognitive impairment, and dementia [14].

This patient had iCAA, a pathological subtype of CAA-related inflammation with perivascular cuffing of inflammatory cells surrounding amyloid-laden blood vessels [15]. Patients like this one develop an acute or subacute syndrome of encephalopathy, focal neurologic signs, headache and seizures. His acute behavioral changes accompanied by aphasia and right facial weakness were thought to represent a manifestation of his underlying disease process although it remains unclear if these were seizures not detected on EEG, cortical spreading depression phenomena, or another mechanism at work. The SDH was attributed to trauma sustained during an episode of agitation rather than the iCAA itself.

Definitive diagnosis of iCAA requires histopathologic confirmation. Probable and possible criteria for diagnosing iCAA are pre-

Table 2

Criteria I	for the	diagnosis	of	iCAA	[16]	·
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Probable	iCAA
1. Age ≥4	40 yrs
2. Presen	ce of ≥ 1 of the following clinical features: headache, decrease in
consci	iousness, behavioral change, or focal neurological signs and seizures;
the pr	esentation is not directly attributable to an acute ICH
3. MRI sh	nows asymmetric unifocal or multifocal WMH lesions
(cortio	cosubcortical or deep) that extend to the immediate subcortical
white	matter
4. Presen	ce of ≥ 1 of the following corticosubcortical hemorrhagic lesions:
cerebi	ral macrobleed, cerebral microbleed or cortical superficial siderosis
5. Absene	ce of neoplastic, infectious, or other cause
Possible	iCAA

MRI shows WMH lesions that extend to the immediately subcortical white matter, otherwise same criteria as above Probable criteria have sensitivities and specificities of 82% and 97%.

respectively, while possible criteria carry a sensitivity and specificity of 82% and 68%, respectively



Fig. 3. Biopsy of the right frontal lobe (A) Thickened small and medium-sized blood vessels are present in the leptomeninges with an associated lymphohistiocytic inflammatory infiltrate. (B) Higher power view shows thickened small blood vessels that are (C) positive for amyloid-beta staining by immunohistochemistry. Hematoxylin and eosin (A and B). Amyloid-beta immunohistochemistry (C). Magnification $200 \times (A)$, $400 \times (B$ and C).

sented in Table 2 [16]. iCAA is usually a monophasic illness, although relapses have been reported [17]. Treatment involves immunosuppressive therapy with most patients being treated acutely with corticosteroids followed in the longer term by cyclophosphamide, methotrexate or mycophenolate mofetil. Our patient was treated with intravenous steroids, followed by cyclophosphamide. The majority of patients show some clinical improvement within 3 weeks of starting treatment [15]. However, not all patients improve and relapses and deterioration have been reported in the literature [18]. Unfortunately, this patient's course involved a relapse and further deterioration despite maximal medical treatment.

This case of iCAA, while rare, exemplifies the diagnostic considerations for a rapidly progressive dementia in the setting of ischemic and hemorrhagic brain lesions with an inflammatory CSF. Given the insensitivity of less invasive methods to differentiate between cancer and autoimmune phenomena – which portend different treatment plans for the patient – brain biopsy remains necessary to firmly establish a diagnosis.

Sources of support

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Competing interests and conflicts of interest

The authors have no competing interests or conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jocn.2017.12.002.

References

[1] Chitravas N, Jung RS, Kofskey DM, Blevins JE, Gambetti P, Leigh RJ, et al. Treatable neurological disorders misdiagnosed as Creutzfeldt-Jakob disease. Ann Neurol 2011;70(3):437-44. <u>https://doi.org/10.1002/ana.22454</u>.

- [2] Sala I, Marquié M, Sánchez-Saudinós MB, Sánchez-Valle R, Alcolea D, Gómez-Ansón B, et al. Rapidly progressive dementia: experience in a tertiary care medical center. Alzheimer Dis Assoc Disord 2012;26(3):267–71. <u>https://doi. org/10.1097/ WAD.0b013e3182368ed4</u>.
- [3] Geschwind MD. Prion diseases. Continuum (Minneap Minn) 2015;21 (6):1612–38. <u>https://doi.org/10.1212/CON.00000000000251</u>.
- [4] Vitali P, Maccagnano E, Caverzasi E, Henry RG, Haman A, Torres-Chae C, et al. Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. Neurology 2011;76(20):1711–9. <u>https://doi.org/10.1212/ WNL.0b013e31821a4439</u>.
- [5] Brown K, Mastrianni JA. The prion diseases. J Geriatr Psychiatry Neurol 2010;23(4):277–98. <u>https://doi.org/10.1177/0891988710383576</u>.
- [6] Sánchez-Enrique C, Vilacosta I, Moreno HG, Delgado-Bolton R, Pérez-Alonso P, Martínez A, et al. Infected marantic endocarditis with leukemoid Reaction. Circ J 2014;78(9):2325–7. Epub 2014 May 30.
- [7] De Tiége X, Héron B, Lebon P, Ponsot G, Rozenberg F. Limits of early diagnosis of herpes simplex encephalitis in children: a retrospective study of 38 cases. Clin Infect Dis 2003;36:1335–9.
- [8] Birnbaun J, Hellmann DB. Primary angiitis of the central nervous system. Arch Neurol. 2009;66(6):704–9. <u>https://doi.org/10.1001/archneurol.2009.76</u>.
- [9] Josephson SA, Papanastassiou AM, Berger MS, Barbaro NM, McDermott MW, Hilton JF, et al. The diagnostic utility of brain biopsy procedures in patients with rapidly deteriorating neurological conditions or dementia. J Neurosurg 2007;106(1):72–5.
- [10] Yamada M. Cerebral amyloid angiopathy: emerging concepts. J Stroke 2015;17 (1):17-30. <u>https://doi.org/10.5853/jos.2015.17.1.17</u>.
- [11] Kimberly WT, Gilson A, Rost NS, Rosand J, Viswanathan A, Smith EE, et al. Silent ischemic infarcts are associated with hemorrhage burden in cerebral amyloid angiopathy. Neurology 2009;72(14):1230–5. <u>https://doi.org/10.1212/ 01.wnl.0000345666.83318.03</u>.
- [12] Scolding NJ, Joseph F, Kirby PA, Mazanti I, Gray F, Mikol J, et al. Abeta-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. Brain 2005 Mar;128(Pt 3):500–15.
- [13] Greenberg SM, Vonsattel JP. Diagnosis of cerebral amyloid angiopathy. Sensitivity and specificity of cortical biopsy. Stroke 1997;28(7):1418–22.
- [14] Maia LF, Mackenzie IR, Feldman HH. Clinical phenotypes of cerebral amyloid angiopathy. J Neurol Sci 2007;257(1–2):23–30.
- [15] Chung KK, Anderson NE, Hutchinson D, Synek B, Barber PA. Cerebral amyloid angiopathy related inflammation: three case reports and a review. J Neurol Neurosurg Psychiatry 2011;82(1):20–6. <u>https://doi.org/10.1136/ innp.2009.204180</u>.
- [16] Auriel E, Charidimou A, Gurol ME, Ni J, Van Etten ES, Martinez-Ramirez S, et al. Validation of clinicoradiological criteria for the diagnosis of cerebral amyloid angiopathy-related inflammation. JAMA Neurol 2016;73(2):197–202. <u>https:// doi.org/10.1001/iamaneurol.2015.4078</u>.
- [17] DiFrancesco JC, Touat M, Caulo M, Gallucci M, Garcin B, Levy R, et al. Recurrence of cerebral amyloid angiopathy-related inflammation: a report of two cases from the iCAβ international network. J Alzheimer's Dis 2015;46 (4):1071-7. <u>https://doi.org/10.3233/iad-150070</u>.
- [18] Hashizume Y, Yoshida M, Suzuki E, Hirayama M. A 65-year-old man with headaches and left homonymous hemianopsia. Neuropathology 2004 Dec;24 (4):350–3.