Rapidly progressive dementia in an elderly man

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A man in his mid-70s presented to an emergency department in Zambia with 2 months of progressive cognitive decline. His family reported that his problems began with an acute episode of nonsensical speech that had resolved within a few hours but with increased lethargy the next day. Within a month, he could no longer hold a coherent conversation about even basic events but remained independent in activities of daily living. His symptoms deteriorated over the next few weeks so that he required assistance with mobility, became increasingly uncooperative and disorientated, could not write his own name, was incontinent, resisted care, would get lost in his house and was no longer able to recognise his family. He had no delusions, hallucinations or headache. His medical history was notable for benign prostatic hyperplasia, type 2 diabetes mellitus and hypertension, which were all well controlled on medication.

At presentation, he was awake and alert, orientated to person only, confabulating and unable to identify family members. His speech was clear but tangential with reduced content. He was fluent with intact repetition. Naming was intact to high-frequency but not low-frequency words. He had ideomotor apraxia and a right homonymous hemianopia. The remaining cranial nerve examination was unremarkable, and motor examination was notable only for paratonia in all limbs. Tendon reflexes were normal, and plantar reflexes were flexor bilaterally. There were frontal release signs, including jaw jerk, palmo-mental, grasp and glabellar tap, but no startle reflex or myoclonus. Sensory, coordination and gait examinations were normal. He had no meningeal signs.

QUESTIONS FOR CONSIDERATION
► What is the likely localisation of his presentation?
► What is the differential diagnosis?
His marked cognitive decline suggested diffuse cortical dysfunction. Frontal release signs suggested frontal lobe involvement while the episode of incoherent speech might suggest a focal seizure localising to Wernicke’s area on the left. Ideomotor apraxia localises to the premotor cortex in the dominant hemisphere, and the right homonymous hemianopia to the left hemisphere, either along the optic tract, at the lateral geniculate body, or in the calcarine cortex.

The rapid decline suggested a rapidly progressive dementia, with a wide differential diagnosis, including vascular (eg, multiple infarcts, thalamic or callosal infarcts, cerebral amyloid angiopathy), infective (eg, viral encephalitis, HIV dementia, urinary tract infections in an elderly person with mild dementia), toxic-metabolic (eg, vitamin B12 and B12 deficiencies, endocrine abnormalities, hyperglycaemia, metal toxicity), autoimmune (eg, central nervous system (CNS) lupus), malignancy/metastasis related (eg, carcinomatous meningitis, paraneoplastic encephalitis), iatrogenic (eg, illicit drug use, chemotherapy), neurodegenerative (eg, Alzheimer’s disease, prion disease, dementia with Lewy bodies) and systemic disease (eg, epilepsy).1 In case series from rapidly progressive dementia referral centres, common causes of rapidly progressive dementia include immune-mediated encephalopathies, prion diseases and neurodegenerative diseases such as Alzheimer’s disease and frontotemporal dementia.1 In other series, secondary reversible causes including infections were most common.2 Though the epidemiology in low-income settings is largely
unknown, these settings might be expected to have higher rates of infective causes.

Creutzfeldt-Jakob disease (CJD) is the prototype of rapidly progressive dementia. Sporadic CJD, the most common form, tends to have early neurological signs. This patient’s visual field deficit did raise suspicion for CJD, although there was no startle response or myoclonus (common findings in CJD). We also considered infective causes of rapidly progressive dementia but these are often accompanied with systemic symptoms such as fever and meninging. Implicated microorganisms include viruses (eg, HIV, herpes simplex), fungal (eg, CNS aspergillosis), spirochaetes (eg, neurosyphilis) and bacteria (eg, CNS tuberculosis). This patient had no systemic symptoms to suggest an infective cause nor was he immunocompromised. Toxic-metabolic causes such as vitamin B12 deficiency should be considered, as should a personal history of exposure to toxins such as organic lead and mercury. However, there was no obvious history to suggest these possible causes.

QUESTIONS FOR CONSIDERATION
► What investigations might further evaluate this patient’s presentation?

Investigations for rapidly progressive dementia includes full blood count with differential; basic metabolic panel including calcium, magnesium and phosphate; HIV test; rapid plasma regain test; liver function and thyroid function tests; rheumatological screen including erythrocyte sedimentation rate, antinuclear antibodies and C reactive protein; urine for urinalysis, toxicology and culture; and cerebrospinal fluids for cell count with differential, protein, glucose, IgG index, oligoclonal bands, venereal disease research laboratory test, 14-3-3 protein, tau, cryptococcal antigen, viral PCRs, Gram stain and bacterial culture, fungal culture, acid-fast bacilli stains and cultures, cytology and flow cytometry. Imaging including MR scan of the brain with and without contrast and chest radiograph should also be obtained. Additional investigations are recommended in some clinical scenarios, including cancer screening, blood smear, homocysteine and additional rheumatologic tests such as anticytoplasmic antineutrophil cytoplasmic antibodies.

Given the resource limitations in our setting, the patient underwent a targeted and stepwise workup that included full blood count, metabolic panel and urinalysis, which were unremarkable. HIV ELISA and PCR were non-reactive. Chest radiograph showed bilateral nodular infiltrates with a small effusion in the left lower lung. MR scan of the brain showed an area of encephalomalacia in the left occipital lobe and generalised brain atrophy. Electroencephalogram (EEG) showed a slowed background rhythm without epileptiform discharges, consistent with moderate encephalopathy. Table 1 details his CSF studies and showed Cryptococcus spp (figure 1). The CSF opening pressure was not measured as there were no manometers available.

We diagnosed cryptococcal meningitis and gave amphotericin B with high-dose fluconazole, because flucytosine, the preferred drug for use in combination with amphotericin B, is currently unavailable in Zambia. He developed complications with acute kidney injury, electrolyte imbalance and congestive heart failure, but these resolved with treatment. He was discharged home on oral fluconazole. His neurological symptoms improved after 3 weeks of treatment to the point where he could recognise his family members, was no longer confabulating and had no ideomotor apraxia.

DISCUSSION
Cryptococcal meningitis arises from an infection caused by the yeast Cryptococcus. The most common pathogens are Cryptococcus neoformans and Cryptococcus gattii, both of which occur naturally in decaying, Table 1 CSF findings

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>White cell count</td>
<td>4 x 10⁹/L</td>
<td>0–5 x 10⁹/L</td>
</tr>
<tr>
<td>Protein</td>
<td>1.64 g/L</td>
<td>0.150–0.45 g/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>2.81 mmol/L</td>
<td>2.20–4.20 mmol/L</td>
</tr>
<tr>
<td>Gram stain</td>
<td>No organisms seen</td>
<td>No organisms</td>
</tr>
<tr>
<td>CrAG-LFA (figure 1)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>India ink</td>
<td>Cryptococcus seen</td>
<td>No cryptococcus</td>
</tr>
<tr>
<td>Xpert MTB/RIF</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Xpert MTB/RIF mycobacterium/resistance to rifampicin. Courtesy of University Teaching Hospital Laboratory.

Figure 1 This patient’s CSF cryptococcal antigen test result. The test was repeated twice to ensure the first unexpected result was not a false positive. Courtesy of University Teaching Hospital Microbiology Laboratory. CSF, cerebrospinal fluid.
deficiencies or a congruence of innate and acquired
includes individuals with undetected innate immune
coccosis in various centres.7 8 This group probably
gitis, between 8% and 81% of patients with crypto-
proportion of patients with cryptococcal menin-
tococcal meningitis who make up a widely variable
of people living with HIV.4 Cryptococcal meningi-
itis is the most common cause of meningitis and one
of the leading causes of death in people living with
in sub-Saharan Africa.5 6 For reasons that are not
clear, most cryptococcal meningitis in people living
with HIV is caused by C. neoformans while C. gattii is
rare in this group but more common in people who are
not immunocompromised. The cryptococcal antigen
in this patient was detected using the CrAg lateral
flow assay (Immy, Norman, Oklahoma, USA), which
cannot differentiate cryptococcal species. The fungus
also grew on Sabouraud’s dextrose agar, but we could
not complete further speciation due to unavailability
of media to identify up to species level in our labora-
tory at the time.

Various studies have shown that the epidemiology,
risk factors, presentations and outcomes of crypto-
coccal meningitis vary between people living with
HIV and those without HIV infection. People without
HIV infection comprise a heterogenous group that
includes recipients of solid organ transplants, people
taking immunosuppressive medications, those with
malignancies and those with poorly controlled
diabetes mellitus. In addition to these groups are
healthy individuals with no obvious risk for crypt-
coccal meningitis who make up a widely variable
proportion of patients with cryptococcal meningi-
gits, between 8% and 81% of patients with crypto-
coccosis in various centres.7 8 This group probably
includes individuals with undetected innate immune
deficiencies or a congruence of innate and acquired
immunodeficiencies. However, new risk factors have
emerged including recreational intravenous drug
use and prolonged influenza virus infection.9 Both
C. neoformans and C. gattii may cause cryptococcal
meningitis in immunocompetent hosts, but C. gattii
characteristically affects this group, accounting for
more than 40% of infections in one study.7

CNS cryptococcosis typically presents as a subacute
tococcal meningitis in most of both people living
with HIV and HIV-uninfected individuals with
features including meningism, fever, headache, focal
neurological deficits and vomiting. However, crypto-
coccal meningitis rarely presents as rapidly progres-
sive dementia and mimicking traditional dementia
syndromes such as Alzheimer’s disease and vascular
dementia.10 11 As such, cryptococcal meningitis may
be misdiagnosed as these non-infective syndromes.

Rapidly progressive dementia has many causes that
are often reversible, and patients need extensive di-
nostic testing to identify treatable causes. However, in
resource-constrained settings with limited diagnostic
capabilities, establishing a definitive diagnosis requires
a prioritised stepwise diagnostic approach focused
on identifying potentially reversible causes. It is also
important in the local setting to have a comprehensive
understanding of the most common causes of rapidly
progressive dementia, as causes differ by region, with
infections likely being more common in low-resource
settings such as Zambia. Therefore, it is important
to exclude infective processes early in the diagnostic
workup.

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