Clinical Reasoning: Myriad manifestations of a global infectious disease

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SECTION 1

A 21-year-old right-handed Cambodian woman with no history of headache presented with 2 weeks of progressive bifrontal headache. She had no sick contacts or recent travel. She moved to the United States at age 3 years. She had no fever, nuchal rigidity, photophobia, phonophobia, nausea, or vomiting. She had a recent history of weight loss and palpitations. There was no tobacco or illicit drug use or high-risk sexual behavior.

She was not pregnant and denied contraception use.

She had a nonfocal neurologic examination. CT head done to rule out acute intracranial pathology showed an abnormality that was followed up by MRI brain with and without contrast (figure 1).

Question for consideration:

1. What are the differential diagnoses to consider?
2. How should we evaluate the patient next?

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Figure 1 CT head shows right insular hypodensity: MRI brain shows restricted diffusion in the right insula with changes seen on T2 fluid-attenuated inversion recovery (FLAIR)

(A) CT head hypoattenuation in the right insular parenchyma (white arrow). (B) Axial diffusion-weighted imaging (DWI) and (C) apparent diffusion coefficient sequences show restricted diffusion in the right subinsular white matter extending to the periventricular white matter along the right temporal horn in the vascular territory of the right middle cerebral artery (D) also seen on FLAIR sequence.

Supplemental data
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SECTION 2

The patient's symptoms of headache and the findings on CT head led us to perform an MRI brain. Findings on MRI included restricted diffusion in the right sub-insular white matter, extending to the periventricular white matter along the right temporal horn, inferior parietal lobe, and frontal temporal operculum, in the vascular territory of right middle cerebral artery, associated with minimal gyriform enhancement or leptomeningeal enhancement, most consistent with early infarcts.

The differential diagnoses for new-onset headache in the setting of cerebral ischemia by imaging studies includes stroke, CNS vasculitis, reversible cerebral vasoconstriction syndrome, and less likely cerebral cortical venous thrombosis (MRI finding of infarct

or hemorrhages typically in nonarterial distribution), meningitis (MRI finding of leptomeningeal enhancement), or encephalitis.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; and Moyamoya syndrome should also be considered in young patients (<45 years) presenting with stroke-like symptoms. Septic emboli in endocarditis leading to septic angiitis should be considered in the appropriate clinical setting.¹

The patient underwent lumbar puncture for further evaluation of a possible vasculitic process. CSF showed protein of 129.6 mg/dL, glucose of 17 mg/dL, 153 leukocytes (62% neutrophils, 32% lymphocytes, and 6% monocytes), 50 erythrocytes, and a negative gram stain. CSF findings of elevated leukocytes with neutrophil predominance, low glucose levels, and elevated protein led us to believe she might have meningitis with vasculitis as a complication. Given the concern for meningitis, she was empirically started on IV antibiotics and acyclovir.

Antibiotics should be initiated immediately even prior to obtaining CSF samples when bacterial meningitis is considered likely. Vancomycin and ceftriaxone are recommended to treat *Streptococcus pneumoniae* and *Neisseria meningitidis*, the 2 most common pathogens in children and adults up to age 50 years. If there is concern for viral encephalitis, acyclovir should be initiated while awaiting herpes simplex virus PCR.² Patients who received dexamethasone (10 mg every 6 hours for 4 days) 15–20 minutes prior to or with the first dose of antibiotics had a significant decrease in unfavorable outcomes.³

Our patient then developed acute left face and arm weakness. She underwent CT angiogram of head and neck to evaluate for vasculitis/craniovertebral dissection. CT angiogram showed segmental narrowing of the right M1 segment of the middle cerebral artery (confirmed later on conventional angiogram) (figure 2A) and incidentally revealed cervical lymphadenopathy (figure 2B). This prompted further imaging in the form of CT thorax, which showed multiple lung nodules and axillary and mediastinal lymphadenopathy (figure 2C).

Question for consideration:

1. How does this incidental finding change the differential diagnosis?
2. What is the next step in management?

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Figure 2 Conventional angiogram shows segmental narrowing in the right M1 segment: CT of the neck and thorax show lymph nodes: CT brain shows tuberculomas

(A) Conventional angiogram shows segmental narrowing (white arrows) of the M1 branch and other areas of constriction and dilation suggestive of vasculitis. (B) CT neck shows a conglomerate of lymph nodes bilaterally, the largest of which was in the right supraclavicular location and measures $1.7 \times 1.8 \times 4.9$ cm (image on the upper right: white arrow). (C) CT of the thorax shows hilar lymphadenopathy and scattered pulmonary nodules. (D) CT head with contrast shows several rim-enhancing masses measuring between 10 and 13 mm located in the region of the anterior communicating, right middle cerebral, and right posterior communicating arteries, suggestive of tuberculomas. There is irregular leptomeningeal enhancement involving the right middle cerebral artery cistern and operculum.

SECTION 3

The differential diagnoses given the findings of multiple lung nodules and cervical and mediastinal lymphadenopathy includes infection (mycobacterial, viral pneumonia, fungal), sarcoidosis, and less likely metastatic disease (thyroid, melanoma, choriocarcinoma, renal).

The next step would be to obtain a lymph node biopsy. Pathology from right supraclavicular lymph node showed acid-fast bacilli (AFB) on the AFB stain (figure e-1 on the *Neurology*[®] Web site at Neurology.org). Hematoxylin & eosin stain showed caseating granulomas consistent with the diagnosis of tuberculosis.

Repeat lumbar puncture showed neutrophilic pleocytosis again, which may be seen during the early phases of tuberculosis (TB) meningitis. Characteristic CSF findings of TB meningitis including lymphocytic pleocytosis (100–500 cells), elevated protein (50–100 mg/dL), and low glucose (<45 mg/dL) can closely mimic bacterial meningitis during the acute phase.⁴

The patient was empirically started on the 4-drug antitubercular regimen rifampin, isoniazid,

pyrazinamide, and ethambutol (RIPE) along with vitamin B₆ and IV dexamethasone to treat pulmonary and CNS tuberculosis.

Among the antitubercular medications, isoniazid and pyrazinamide have excellent CNS penetration. Isoniazid and rifampin are administered for a total duration of 9–12 months for CNS tuberculosis; pyrazinamide and ethambutol are administered for 2 months at initiation of therapy.

On day 4, the patient was found to be lethargic and poorly responsive. There were no new neurologic deficits. Repeat CT head did not reveal any new changes. EKG showed polymorphic ventricular tachycardia consistent with Torsades de Pointes (figure e-2). Her baseline EKG had a prolonged QTc of 490 ms with sinus bradycardia and intermittent junctional rhythm.

Question for consideration:

1. What are the potential causes for her cardiac dysrhythmia?

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SECTION 4

Torsades de Pointes may be seen with electrolyte abnormalities—hypokalemia, hypomagnesemia, hypocalcemia; drugs—antiarrhythmic, antihistamine, antimicrobial, psychiatric drugs; genetic long QT syndromes; bradyarrhythmias; anorexia nervosa; and cerebrovascular diseases including subarachnoid hemorrhage and stroke.⁵

About 6% of patients die of sudden death of unknown cause within 30 days after an acute stroke. Brain injuries, especially subarachnoid hemorrhage and stroke, may cause an alteration in the autonomic nervous system that could then potentially lead to cardiac dysrhythmias and sudden cardiac death. EKG abnormalities include rhythm disturbances such as atrial fibrillation and ventricular arrhythmias. QT interval prolongation, ST segment, T-wave changes, and left axis deviation have also been observed. EKG changes occur due to involvement of limbic

system, diffuse subcortical autonomic centers, and hypothalamus when a stroke affects the nondominant insular cortex (as in our patient).⁶

Our patient's potassium levels were low (2.8 mmol/L), which was corrected. She had received a dose of haloperidol 24 hours prior, which can potentially prolong the QTc; this was stopped.

Despite all corrections, the patient continued to have ventricular arrhythmias, likely secondary to the nondominant insular stroke, and was placed on defibrillator and discharged on the 4-drug antitubercular regimen in a stable condition.

She returned a week later with worsening headache, photophobia, and blurred vision.

Question for consideration:

1. What are the potential causes of her new symptoms?
2. What do you identify on the CT head (figure 2D)?

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SECTION 5

The potential causes for a patient with CNS tuberculosis and acute worsening of headache would include worsening tubercular meningitis or vasculitis, raised intracranial pressure secondary to hydrocephalus, or tuberculomas. TB vasculitic infarcts commonly occur in the caudate, genu of the internal capsule, and anterolateral thalamus, as compared to atherosclerotic infarcts, which tend to occur in the posterior limb of the internal capsule, lentiform nucleus, and the posterolateral thalamus.

CT head with contrast showed multiple tuberculomas. The patient was treated with broader spectrum antibiotic coverage including amikacin, moxifloxacin, and linezolid. Rapid genotype testing was negative for resistant disease. She was continued on 4-drug antitubercular therapy and moxifloxacin.

The patient's headache improved with IV opiates and she was discharged and enrolled into the Direct Observational Therapy program with the Department of Health. She remained symptom-free during subsequent evaluation.

DISCUSSION Tuberculomas could occur in about 10% of patients with TB meningitis. Lesions may be solitary but are often multiple and typically have surrounding edema and ring enhancement. Tuberculomas could occur in the brain, spinal cord, or subdural, subarachnoid, or epidural space.⁷

Occurrence of tuberculomas despite being on 4-drug anti-TB regimen should raise suspicion of immune reconstitution inflammatory syndrome (IRIS). IRIS can unmask a subclinical infection or cause recurrence of a previously treated infection. Steroids are indicated for treatment of tuberculosis as well as for prevention of IRIS. Prolonged duration of treatment and slower tapering is recommended to avoid clinical deterioration.^{7,8}

CDC and prevention surveillance reports show that there has been a decrease in incidence of new TB cases reported in the United States, of 2.2% between 2013 and 2014. Over the last 10 years, this rate is the smallest decline. Foreign-born persons in the United States have a 13.4 times higher rate than US-born persons. Among the foreign-born, Asians have the largest number of TB cases, the rate being 28.5 times higher compared to non-Hispanic whites.

Rates among non-Hispanic blacks and Hispanics are about 8 times higher each.⁹

TB is typically thought to be a disease of the tropics but does affect individuals in the United States. This case highlights the various manifestations of tuberculosis in a single patient—meningitis, vasculitis, and tuberculomas. This case also brings to light the effect of a lesion or stroke in the nondominant insular cortex on the autonomic nervous system.

AUTHOR CONTRIBUTIONS

Dr. Prabhu drafted and compiled the original manuscript, made revisions, interpreted neuroradiologic aspects of this article, and added professional comments. Dr. Raghupathi assisted in drafting, revised the manuscript for intellectual content, interpreted neuroradiologic aspects of this article, and formatted the figures. Dr. Dissin revised the manuscript for intellectual content and added professional comments.

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