Clinical Reasoning:

A case of Wegener granulomatosis complicated by seizures and headaches

Curiouser and curiouser

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SECTION 1

A 19-year-old man presented with a 5-day history of vomiting and passing dark urine. He gave a 6-month history of arthralgias and joint swelling, particularly affecting larger joints. He had recurrent epistaxis and recent episcleritis. He was noted to be thin and pale, with conjunctival suffusion and deformity of his nasal bridge. He was normotensive (115/60 mm Hg) and afebrile (35.5°C). Blood parameters revealed normocytic normochromic anemia and acute renal failure. Renal biopsy showed extensive crescent formation with segmental necrotizing inflammation and fibrin deposition of the glomeruli. cANCA was strongly positive (titer 1280; ELISA PR3+) and he was diagnosed with Wegener granulomatosis. He commenced hemodialysis, steroids, and oral cyclophosphamide, and he was discharged home.

One month later, he presented with acute onset of throbbing headaches associated with nausea and photophobia, as well as recurrent generalized seizures necessitating sedation and intensive care unit admission. He was pyrexia (38°C) and hypertensive (165/95 mm Hg). Renal indices were abnormal (urea 29.1 mmol/L; creatinine 755 µmol/L; potassium 5.4 mmol/L). Clinical examination revealed no focal neurologic deficits.

Initial noncontrast brain CT was normal. Brain MRI with gadolinium showed small, ill-defined, nonenhancing high signal areas measuring 5–20 mm in several locations (figure, A).

Questions for consideration:

1. What are the possible etiologies of the changes on brain MRI?
2. What additional diagnostic testing would you consider at this point?

Figure Brain MRIs

(A) Axial fluid-attenuated inversion recovery (FLAIR) brain MRI showing small, ill-defined, nonenhancing high signal areas measuring 5–20 mm in several locations. (B) Axial FLAIR brain MRI showing progression in radiologic changes over a further 1-month interval. Bright confluent lesions are seen in both parieto-occipital regions. (C) Axial FLAIR brain MRI showing marked progression in radiologic changes over a further 2-month interval. Bright confluent areas are seen extensively involving the occipital and parietal lobes, and including the frontal lobes. (D) Axial FLAIR brain MRI showing full resolution of radiologic changes 6 months after commencement of IV cyclophosphamide.

GO TO SECTION 2

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SECTION 2

Full septic screen including midstream urine, chest x-ray, echocardiogram, and blood cultures were negative for active infection. MR angiography and formal four-vessel angiography were normal and revealed no beading. Postictal EEG was normal. A lumbar puncture was declined by the patient. He was commenced on oral phenytoin with titration of his immunosuppression and discharged home.

He was readmitted 1 month later with further seizures and neutropenic sepsis. He was normotensive (120/60 mm Hg) and pyrexia (38.6°C). Neurologic examination was within normal limits. Focal areas of abnormal high signal were again noted on brain MRI and were identical to those previously reported (figure, A). ANCA levels were low (1:80). Cyclophosphamide was discontinued and mycophenolate was commenced. He was again admitted 1 month later with pyrexia (38.5°C) and diarrhea. He described brief episodes of visual blurring and central loss of vision. No evidence of central scotoma was detected clinically. Brain MRI now showed more extensive areas of high signal in both parieto-occipital regions (figure, B). CSF analysis showed normal protein and glucose parameters and was

acellular. Testing for JC Virus was negative. He commenced antimicrobial therapy and his immunosuppressive therapy was increased.

He presented again 2 months later with recurrent partial seizures and severe throbbing headaches characteristic of migraine with aura. He described episodes of body image distortion (macrosomatognosia) with his hand “ballooning,” colored visual spectra phenomena characterized as a “kaleidoscope” effect or a light moving diagonally across his visual field from left to right, and an impaired sense of passage of time (a perceived increased speech velocity). These episodes heralded the onset of headache, seizures, or a combination of both. He had intractable hiccups and episodes of vertigo, ataxia, slurred speech, and nystagmus. He was normotensive (100/60 mm Hg), pyrexia (38.6°C), and neutropenic. Serum antiepileptic drug levels were within normal limits and cANCA was negative.

Questions for consideration:

1. What is the term coined for the symptoms he is describing?
2. What is the postulated anatomic basis of his symptoms?

GO TO SECTION 3

SECTION 3

The clinical picture at this stage was thought consistent with the Alice in Wonderland syndrome (AIW). The features of AIW were first reported by Coleman in 1932,¹ but it was Todd² who coined the term in 1955 to describe the phenomena of distorted space, time, and body image. Lewis Carroll made this phenomenon famous in “Alice’s Adventures in Wonderland” (1865) and it has been suggested that Alice’s transformations were based on Carroll’s own migraineous symptomatology; however, this remains controversial.^{3,4} AIW has been associated with migraine, epilepsy, drug intoxication, cerebral mass lesions (particularly involving the occipital and temporoparietal lobes), psychiatric disease, viral infections, pyrexia, and vasculitis.^{5,6} Perceptual errors of body schema and objects (kinesthetic illusions or metamorphopsia), of people appearing smaller (micropsia) or bigger (macropsia) than normal, visual hallucinations (Lilliputian hallucinations), and acceleration or deceleration of the passage of time have been attributed to AIW. It may also be associated with vertigo.⁷ The etiology and anatomic basis are

not fully understood. Body image distortion, vertigo, and metamorphopsia have been described from posterior parietal stimulation.⁸ Positive visual phenomena of flashing lights and colored visual spectra equated to a kaleidoscope and negative visual phenomena (scotoma) are both established occipital lobe phenomena. In addition, headache and vomiting may have an occipital origin.⁹

These symptoms prompted more brain imaging. Brain MRI showed diffuse white matter high signal abnormalities demonstrating dramatic interval progression involving the occipital, parietal, and temporal lobes in addition to bilateral cerebellar lesions with no enhancement with gadolinium (figure, C).

The differential diagnosis of the underlying pathologic etiology was reversible leukoencephalopathy syndrome (RPLS) vs active cerebral vasculitis.

Questions for consideration:

1. How would you manage a patient with Wegener granulomatosis, cerebral complications, and recurrent neutropenic sepsis?
2. How would you monitor response to treatment?

GO TO SECTION 4

SECTION 4

He was commenced on a modified dose of IV cyclophosphamide with close monitoring of bone marrow suppression. Sepsis and fluctuations in blood pressure were aggressively treated. Seizure control required quadruple antiepileptic drug therapy. Response to treatment was monitored by clinical status and serial C-reactive protein and c-ANCA measurements. Six months later he is well with full resolution of the radiologic changes (figure, D), seizures, and headaches. He remains dependent on dialysis.

DISCUSSION We present a patient with cANCA-positive renal failure associated with progressive but reversible symmetric FLAIR-bright brain MRI lesions who developed features of AIW syndrome. The differential diagnosis initially included an infectious etiology, progressive multifocal leukoencephalopathy, Neuro-Behçet disease, acute disseminated encephalomyelitis, multiple sclerosis, cerebral vasculitis, and RPLS. CSF analysis showed no abnormalities suggesting inflammation, infection, or malignancy. MR and catheterization angiography revealed no evidence of vasculitis, although this would not completely exclude CNS vasculitis as Wegener disease typically affects small and medium vessels, which are not formally assessed by these methods. Serial brain MRI with gadolinium revealed no enhancement, however, also favoring a diagnosis of prolonged RPLS precipitated by renal failure, sepsis, and possible transient changes in blood pressure, not captured clinically.

RPLS is caused by subcortical white matter edema predominantly involving the posterior regions of the brain, but gray matter and other regions including the brainstem and cerebellum may be involved. Although this is usually recognized as a single event,

recurrent episodes have been reported.¹⁰ The duration and recurrence of symptoms over a 4-month period despite changes in immunosuppression is atypical, and, despite instigation of these measures, there was clinical and radiologic progression. Aggressive immunosuppression was recommenced, albeit at modified doses, resulting in full resolution of symptoms and radiologic changes. We propose that the amended dosage of cyclophosphamide immunotherapy induced disease remission salvaging residual intrinsic renal function, reducing subclinical systemic blood pressure alterations, while reducing the risk of sepsis and direct chemotoxic effects of this therapy and thus improving cerebral autoregulation.

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