A Man with Worsening Legs Instability

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A 40-year-old Thai man residing in Nakhon Ratchasima Province, Thailand.
Occupation: general employee

Chief Complaint

Worsening legs instability for 2 months

History of Present Illness

5 months ago: He began to experience gradually onset of muscle instability in both legs. He reported that he had a limp along with difficulty with balance. The severity of the instability in both legs was symmetrical without abnormal sensation and pain in any muscles. Difficulty in balance, constant during the day and night. He is still able to do his normal daily activities. He denied fever, headache, dizziness and visual disturbance. Urinary and bowel functions were normal.

2 months ago: His difficulty with balance has worsened, affecting his mobility. He has never had muscle aches and both arms can function normally. He denied dysphagia, diplopia, dyspnea and aspiration symptoms.

Past and Personal History

- Occasional smoking and drinking
- Refused to use vasoconstrictive drugs compound

Family History

- No reported history of muscle weakness or stroke-like symptoms in any family members

Physical Examinations

General appearances: A Thai aged man, normosthenic build, alert and active

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Vital signs: BT 36 C, HR 70 bpm, RR20 tpm, BP104/72 mmHg

HEENT: pink conjunctivae, anicteric sclerae, no parotid and thyroid gland enlargement, no carotid bruit

Heart and lungs : unremarkable

Abdomen: soft, not tender, no hepatosplenomegaly

Extremities: pruritic papular eruption on both legs, no edema, radial and pedal pulses are symmetric

DRE: normal sphincter tone

Neurological examinations

Consciousness: Alert and active, follows commands, oriented to time, place, and person

Cranial nerves:

CN I: equally sense of smell, **CN II**: pupil 2mm RTLBE, pupil direct and consensual light reflex were normal with negative RAPD, no visual field defect, **CN III, IV, VI**: extraocular muscle movements were intact, **CN V**: normal facial sensation, intact corneal reflex, normal mastication muscles, **CN VII**: no facial palsy, **CN VIII**: intact, **CN IX, X**: equally palatal movement, positive gag reflex, centrally positioned uvula, **CN XI**: head turning and shoulder shrugging were intact, **CN XII**: normal tongue movement, no tongue atrophy

Motor: mild atrophy both legs without spasticity, normal muscle tone, motor power grade V in upper extremities and grade IV+ both proximal and distal parts in lower extremities

Sensory: intact pinprick, fine touch and proprioception

DTR: 2+ for all extremities

Cerebellar signs: spontaneous horizontal nystagmus with increased amplitude while moving EOM in both eyes, minimally bilateral impaired FTNF test, dysdiadokokinesia, impaired Tandem gait and HTK test, No truncal ataxia, No slurred speech

Babinski and clonus: negative

Meningeal signs: no stiffness in the neck

Cortical signs: normal motor speech, comprehension and repetition, no hemineglect

Problem lists

1. Progressive paraparesis without bowel and bladder involvement
2. Bilateral cerebellar hemispheric dysfunction
3. Suspected HIV infection

Discussion

A young male patient presented with gradually onset progressive leg weakness accompanied by an unsteady gait. Upon examination, decreased motor power in the legs was observed equally, without sensory and bulbar involvements. Characteristics of weakness are a loss of muscle coordination rather than a loss of power to exert effort. The anatomical lesion is likely to be in cerebellar regions or its connections. And the pathology of the disease is likely to be a diffuse inflammatory process rather than a mass-like because the lesions appear to recur with the duration of the disease progression. Important objective evidence that allows the neurological lesion to be considered further is the detection of a pruritic papular eruption rash on both legs that the patient was not concerned. The appearance of the rash suggests that the patient may be immunocompromised. The mechanism behind the progressive paraparesis is most likely secondary to an opportunistic CNS infection. The possible differential diagnosis includes JC virus infection, herpes viral encephalitis, toxoplasmic

encephalitis, neurosyphilis, primary CNS lymphoma, and autoimmune encephalitis.

Investigations

Complete blood count: Hb 13.2 g/dL Hct 40.1% WBC 3600 10*3/uL (N48% L38%) Plt 264 10*3/uL

Syphilis test: RPR non-reactive, **HIV antibody:** Reactive**

Liver function test: TP 8.5 g/dL, Glo 4.2 g/dL, Alb4.3 g/dL, TB 0.6 mg/dL, DB 0.3 mg/dL, AST 53 U/L, ALT 60 U/L, ALP 71 U/L

Electrolyte: Na 137.2 mmol/L, K4.34 mmol/L, Cl 104 mmol/L, HCO3 22 mmol/L

Creatinine 1.03 mg/dL, eGFR 90.4 ml/min/ 1.73m^2

Thyroid function test: FT3 1.77 pg/mL, FT4 0.86 ng/dL, TSH 1.013 mIU/L

HBs Ag, Anti-HBs, Anti-HCV: non reactive

CSF profile: opened pressure 12 cmH_2O, Closed pressure 11 cmH2O, Colorless and clear, pH 8.0, Specific Gravity 1.005, RBC 0 cell/uL, WBC 7 cell/uL, (L 99%, N1 %), protein 58.2 mg/dL, sugar ratio 60%, Gram, AFB and India ink were negative. Culture was negative

CSF PCR for the JC virus: detectable**

CSF PCR for HSV: undetected, **CSF-VDRL**: non-reactive

EKG: normal sinus rhythm, rate 85 /min regular, no ischemic pattern, no chamber enlargement

CXR: normal cardiothoracic ratio, normal parenchymal of both lungs

MRI brain (figure 1): Asymmetric hypointense signal on T1W (upper row) and hyperintense signal on T2W and T2W/FLAIR (middle and lower rows) in bilateral cerebellar peduncles, bilateral cerebellar hemispheres and brainstem without restricted diffusion of enhancement. No evidence of vasogenic edema or pressure effect. The multiple punctate foci and patchy hyperT2W/FLAIR lesions without restricted diffusion or enhancement at both centrum semiovale and periventricular white matter (not shown)

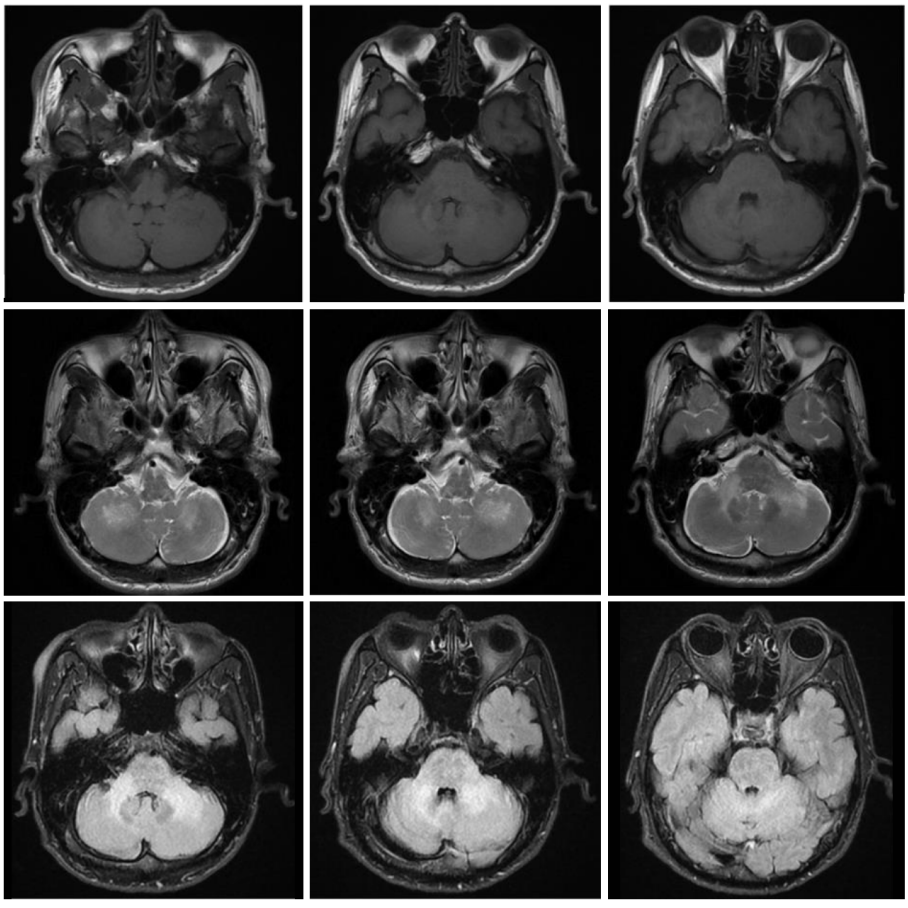

Figure 1 MRI brain (Front cover)

Diagnosis: Progressive multifocal leukoencephalopathy (PML)

Progress note: Based on the medical history, examination, and laboratory results mentioned above, it was revealed that the patient does not have any infection aside from PML. He was promptly and initially treated with Highly Active Antiretroviral Therapy (HAART). His leg weakness gradually improved to the point where he was able to resume walking. During the follow-up treatment, the patient was able to return to normal work, though he still experienced postural tremors and uncoordinated movements. He could walk, and the power of his muscles was graded as V in all extremities.

Conclusion: PML is a neurological disease caused by the JC virus infecting the brain parenchyma. Although PML is rare in general practice, its prevalence has been found to increase, especially in immunocompromised patients.

PML

PML is a rare and frequently fatal demyelinating disease of the CNS, primarily affecting individuals with compromised immune systems. It is caused by the infection of the polyomavirus JC (JCV) in oligodendrocytes.[1,2] Asymptomatic initial infection with JCV happens during childhood, and antibodies can be detected in 86% of adults. [3] In the context of significant cellular immunosuppression, JCV may undergo reactivation, potentially resulting in genomic rearrangement and the emergence of neurotropic variants capable of replicating within glial cells.[3]

This occurs despite the typical latency of the virus in the kidneys and lymphoid organs in the majority of individuals.[4] The virus can subsequently disseminate to the brain, where it initiates a lytic infection of oligodendrocytes, the cells responsible for producing myelin in the central nervous system.[3] Both the subcortical white matter and the cortex are affected by PML-associated demyelination. Infection of cortical neurons by JCV is responsible, and demyelinating lesions of PML often encompass gray matter.[5,6]

Classic PML typically presents with subacute neurological deficits, encompassing altered mental status, motor deficits such as hemiparesis or monoparesis, limb ataxia, gait ataxia, and visual symptoms like hemianopia and diplopia. It is noteworthy that PML may exhibit asymptomatic features during its initial stages.[7,8] PML typically spares the optic nerves and spinal cord. Nevertheless, there was a reported case of PML restricted solely to the spinal cord in one patient, as detected postmortem. Additionally, incidental discovery of PML lesions in the spinal cord was noted during the postmortem examination of another patient with HIV infection who succumbed to hemispheric PML.[9]

In neuroimaging studies, the typical presentation of PML includes distinct unilateral or bilateral demyelinated foci that do not adhere to cerebrovascular territories. These lesions demonstrate an absence of mass effect or contrast enhancement. Primarily, PML lesions emerge in the subcortical white matter of the parieto-occipital or frontal lobes, though the involvement of additional regions such as the corpus callosum, brainstem, pyramidal tracts, and cerebellum is also observed.[10-12] In up to 17% of cases, deep gray structures such as the basal ganglia and thalamus may be involved, although this manifestation consistently co-occurs with white matter disease.[13] Lumbar puncture coupled with polymerase chain reaction (PCR) analysis serves as the cornerstone for diagnosing PML in individuals manifesting clinical and neuroimaging findings consistent with the condition. The definitive identification of PML is achieved through the detection of JCV DNA within the cerebrospinal fluid via PCR analysis. Thus, PCR represents the optimal modality for validating the diagnosis of PML.[7]

Immune reconstitution is pivotal in managing PML, as there is currently no specific treatment available, and the condition carries a high mortality rate. Therefore, the primary therapeutic approach focuses on restoring the host's adaptive immune response, which has been shown to prolong survival. The implementation of this strategy varies depending on the clinical context:

- For patients with HIV infection: initiating or optimizing effective antiretroviral therapy (ART).
- For patients without HIV infection: withdrawal of immunosuppressive drugs, if feasible.
- For patients with natalizumab-associated PML: discontinuation of natalizumab, a medication used in multiple sclerosis treatment, and initiation of plasma exchange.

Learning point from internship:

As an intern doctor, encountering cases of progressive weakness like the one presented here reinforces the importance of a systematic approach to neurological symptoms. Firstly, it's crucial to conduct a detailed history, paying attention to the onset, progression, associated symptoms, and any underlying medical conditions such as HIV infection in this case. A thorough physical examination focusing on neurological signs, including cranial nerves,

motor, sensory, cerebellar, and reflex assessments, helps localize the lesion and guide differential diagnosis. In cases of progressive weakness, integrating clinical findings with appropriate diagnostic tests such as MRI imaging and cerebrospinal fluid analysis plays a pivotal role in narrowing down potential etiologies. This multidisciplinary approach involving neurology, infectious diseases, and radiology specialists ensures comprehensive evaluation and timely intervention. Furthermore, the experience underscores the significance of maintaining a high index of suspicion for opportunistic infections in immunocompromised patients, emphasizing the need for early initiation of specific therapies tailored to the underlying cause, as seen with the prompt administration of HAART in this instance. Ultimately, this case reinforces the internship learning experience by highlighting the intricate interplay between clinical acumen, diagnostic process, and collaborative patient management in navigating complex neurological conditions such as PML.

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