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Progressive Multifocal Leukoencephalopathy and *Acinetobacter Baumannii* Bacteremia in a Human Immunodeficiency Virus-Infected Patient -Case Report and Literature Review

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a rare disease entity predominantly observed in patients infected with human immunodeficiency virus (HIV). The clinical outcome is frequently devastating if the diagnosis is delayed. In the era of combination antiretroviral therapy (cART), the incidence has declined. Poor adherence to HIV medication, often seen in patients of low socioeconomic status, continues to drive disease progression and the subsequent development of PML. Here, we present a patient with weakness and cognitive impairment who was diagnosed with PML based on characteristic magnetic resonance imaging (MRI) findings and detection of John Cunningham (JC) virus in the cerebrospinal fluid via polymerase chain reaction (PCR). During hospitalization, the patient also developed primary *Acinetobacter baumannii* and Methicillin-susceptible *Staphylococcus aureus* (MSSA) bacteremia. This case underscores the critical importance of skin disinfection and infection control measures during intravenous catheterization. The patient was initiated on cART and appropriate antibiotics shortly after admission. Fortunately, no immune reconstitution inflammatory syndrome (IRIS) occurred. Following a prolonged hospital stay, his motor function improved significantly, progressing from an inability to walk to independent ambulation with a walking aid.

Key Words: progressive multifocal leukoencephalopathy, HIV, *Acinetobacter baumannii*

Introduction

PML is a rare disease entity. It occurred in immunocompromised patients, primarily those with HIV infection. Patients with multiple sclerosis undergoing natalizumab treatment, organ transplant recipients, and those with hematological malignancies constitute a smaller proportion. PML is caused by JC virus, a type of Polyomavirus. It typically

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causes an asymptomatic infection during childhood and reactivates when the patient becomes immunocompromised. In advanced-stage HIV-infected patients, reactivation frequently manifests as motor weakness, cognitive impairment or ataxia. Without treatment, the disease progresses rapidly and is ultimately fatal. cART can restore immune function and halt disease progression if administered in time. Although the accessibility and availability of cART have decreased the incidence of PML, cases still occur among late presenters and patients with poor adherence to therapy. Here, we present a case of HIV-infected patient with low socioeconomic status and poor adherence who developed PML and *Acinetobacter baumannii* bacteremia, along with a review of the associated literature.

Case report

A 34-year-old homeless man crawled to a police station seeking help and was subsequently transported to our emergency department (ED). He complained of bilateral leg weakness and poor oral intake, accompanied by incoherent speech for two weeks. In the ED, impaired cognitive function was noted. His body temperature was 36.8°C. Laboratory data revealed a white blood cell count of 3,800 / μL, a C-reactive protein level of 3.4 mg/dL, a hemoglobin level of 8.8 g/dL, a serum creatinine level of 1.1 mg/dL, and a potassium level of 2.3 mmol/L. Brain computed tomography (CT) revealed findings suspicious for acute ischemic stroke in the left parietal and occipital lobes and the right cerebellum. He was admitted under the suspicion of acute ischemic stroke and hypokalemia.

Upon admission, MRI demonstrated an abnormal linear high-signal intensity in the left parieto-occipital lobes on diffusion-weighted imaging (DWI) and hyperintensity signal on T2-weighted image (Fig 1). Regarding his medical history, he had been diagnosed with HIV infection five years ago, with irregular follow-up at another hospital. Consequently, HIV-related workups were performed, showing a serum rapid plasma reagin (RPR) of 1:16, positive treponemal chemiluminescence immunoassays, a CD4 count of 4 /μL, and an HIV viral load of 70,779 copies/mL. Lumbar puncture revealed cerebrospinal fluid (CSF) with a WBC of 1 /μL, Glucose of 54 mg/dL (40-70), protein of 47.6 mg/dL (15-45),

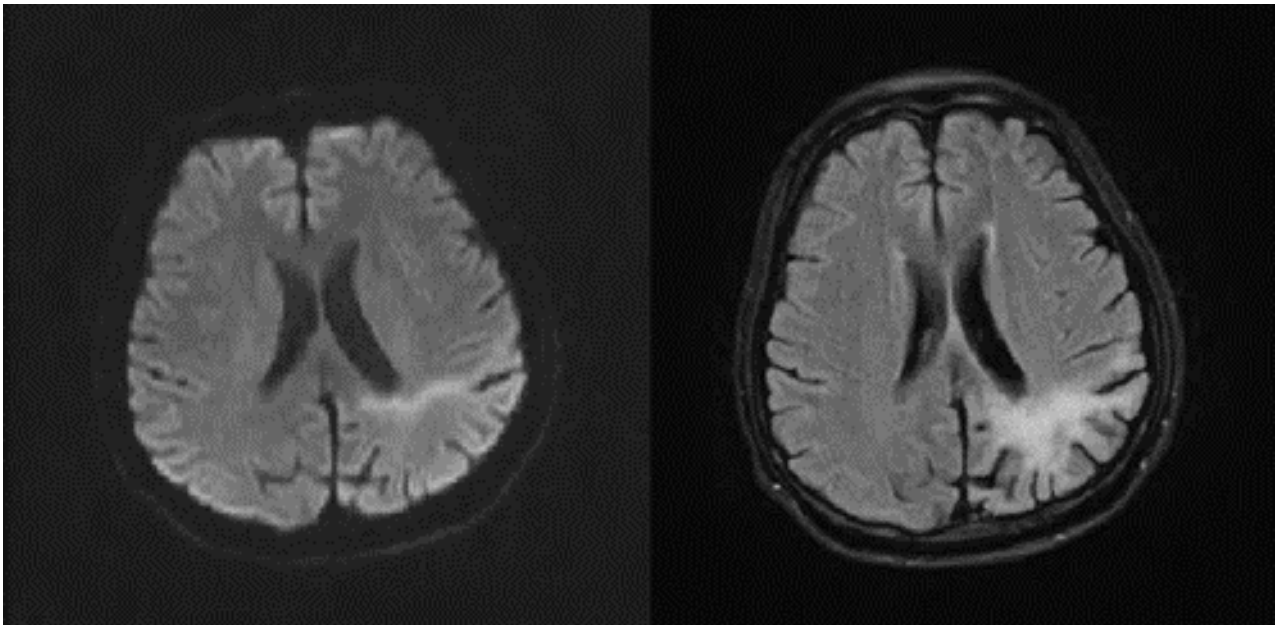

Fig. 1. MRI reveals a hyperintense signal in the left parieto-occipital lobes on diffusion-weighted imaging (left) and T2-weighted/ fluid attenuated inversion recovery (FLAIR) imaging (right).

and adenosine deaminase (ADA) of 1 U/L. India ink stain, Gram stain and acid-fast bacilli (AFB) stain were all negative. Cryptococcus antigen was negative. The meningitis multiplex PCR panel (including Cytomegalovirus(CMV), Varicella-zoster virus, *Escherichia coli*, *Hemophilus influenza*, *Listeria monocytogenes*, *Neisseria meningitides*, Enterovirus; human simplex virus-1, human simplex virus-2, human herpes virus-6; *Streptococcus pneumonia*; *Cryptococcus neoformans*)returned all negative results. CSF Tuberculosis (TB) PCR was negative, and the CSF venereal disease research laboratory (VDRL) test was non-reactive. Additionally, *Toxoplasma gondii* IgG was negative. Under the tentative diagnosis of PML, a CSF sample was send to the laboratory for JC virus PCR testing. Despite the non-reactive VDRL, neurosyphilis could not be entirely excluded due to elevated CSF protein levels. Accordingly, intravenous ceftriaxone (2 gm every 12 hours) was initiated. Six days later, the JC virus PCR result was positive (Fig. 2), and subsequent genome sequencing confirmed compatibility with JC virus. On day 3 of admission, the patient developed a high fever (39°C), chest X-ray revealed mildly increased bilateral infiltrates, and blood culture was obtained for fever evaluation. Empirical treatment with sulfamethoxazole/trimethoprim was initiated despite the absence of desaturation or shortness of breath. Fever subsided after two days. Blood culture drawn on Day 3 revealed growth of MSSA and *Acinetobacter baumannii* five days later, both susceptible to sulfamethoxazole/trimethoprim. Nerve conduction velocity (NCV) studies of the lower limbs showed L4/L5 radiculopathy. Aspirin and normal saline were prescribed on admission, followed by cART for HIV starting from Day 3. Benzathine penicillin was administered intramuscularly weekly for three doses. Sulfamethoxazole/trimethoprim was continued for MSSA and *Acinetobacter baumannii* bacteremia based on sensitivity results. After a 22-day hospitalization, follow-up blood culture remained sterile, the patient's mental status improved, and he was able to ambulate under supervision. He was subsequently discharged to a long-term care facility for further care and scheduled outpatient follow-up.

Discussion

JC virus, also known as human Polyomavirus 2, causes asymptomatic infection in most individuals. It may spread insidiously via the oral or respiratory routes, and its seroprevalence increases with age. The anti-JCV antibody seroprevalence has been reported as 47% among individuals aged 15–29 years, 59% among 40–49 years, and 64% for individuals older than 60 years[1]. The virus can persist in the kidneys, lymphoid tissue, and bone marrow, and is shed in the urine[2]. When the host becomes immunocompromised and cellular immunity decreases, the latent virus (archetype) replicates, undergoes genomic rearrangement (prototype) and becomes neurotropic. The reactivated virus reaches the brain

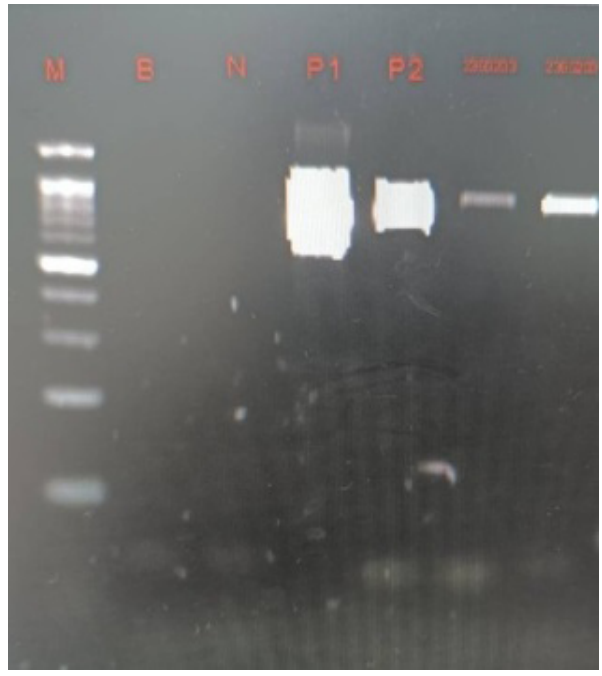

Fig. 2. JC virus PCR Gel electrophoresis results. The existence of JC virus in cerebrospinal fluid was confirmed. (Lane 1: marker; Lane 3: negative control; Lane 4- 5: P1/P2 positive control; Lane 6-7: patient samples)

tissue via infected leukocytes through the inflamed blood-brain barrier or directly through peripheral nerves. Upon reaching the brain, it infects oligodendrocytes, astrocytes, cerebellar granule cells and even neurons. It causes demyelination, enlarged oligodendrocyte nuclei and bizarre astrocytes with lobulated nuclei, a combination called the histopathologic triad. According to a prospective cohort, after the initiation of cART in 1997, the incidence rate of PML declined by 57%, from 1.15 (95% confidence interval [CI], 0.98–1.31) in the period 1997–2000 to 0.49 (0.37–0.61) per 1000 person-years in 2009-2011[3]. In another large epidemiological survey conducted in France, the incidence of PML from 2010 to 2017 was stable during the study period at 0.11 per 100,000 person-years (95% CI 0.10–0.12)[4]. The continued decline in incidence may be due to the widespread accessibility and prevalence of cART. The predominant underlying conditions associated with PML were HIV infection (43.7%), followed by hematological malignancies (21.9%), chronic inflammatory diseases (20.2%), solid organ transplantation (4.3%), solid neoplasm (4.1%) and primary immune deficiency (1.5%)[4]. According to a large prospective cohort study involving 97,905 HIV-infected patients, the risk factors for PML included starting cART within the past 6 months, intravenous drug user (IDU), and hepatitis C virus (HCV) seropositivity[3]. PML occurrence within 6 months of cART initiation may result from immune restoration, presenting as unmasking IRIS. Clinically, patients may manifest sensory loss, weakness, dysarthria, ataxia, cognitive impairment, and hemianopsia, with motor weakness and cognitive dysfunction being the most frequently encountered symptoms[5]. Lesions typically involve the subcortical to deep white matter and may extend to gray matter[6]. The lesion borders are sharp toward the cortex but blurred toward the white matter[7]. MRI reveals high-signal intensity on T2-weighted images in patients with PML and DWI may determine if the lesion is actively expanding[7]. Bilateral and supratentorial involvement occurs most frequently, with the parietal and frontal lobes being the two most commonly affected regions. In addition to clinical symptoms and typical imaging findings, the diagnosis of PML relies on a positive PCR result for JC virus in the CSF or histopathological confirmation

Table 1. Timeline of key events and treatment

Date	Key Events and Treatment
2024.09.16	General weakness and incoherent speech for 2 weeks. Brain CT at ED showed suspected stroke; admitted for further evaluation
2024.09.16	Brain MRI performed
2024.09.18	ID consultation; initiated anti-retroviral therapy (ART)
2024.09.18	Spiking high fever; blood cultures obtained; started empirical sulfamethoxazole/trimethoprim (TMP/SMX).
2024.09.19	Lumbar puncture performed; CSF sent for JCV PCR testing.
2024.09.19	Initiated IV Ceftriaxone 2gm Q12h for suspected neurosyphilis (total 9-day course)
2024.09.23	Blood culture grew MSSA and *Acinetobacter baumannii*, continued TMP/SMX based on susceptibility results
2024.09.23	Started treatment for late latent syphilis: Benzathine penicillin 2.4MU IM weekly for 3 weeks
2024.09.25	CSF JCV PCR reported positive
2025.09.25	Follow-up blood culture showed no growth (sterile)
2025.10.07	Discontinued TMP/SMX and discharged

in brain tissue. Although the sensitivity of JC virus PCR tests varies, the American Academy of Neurology diagnostic criteria state that the sensitivity of newer ultrasensitive techniques (detecting as few as 10 copies/mL of CSF) is >95%[8]. The primary treatment strategy for PML focuses on restoring host immunity. Due to the absence of animal models and the difficulty of culturing the virus *in vitro*, effective anti-JC virus therapies remain lacking[9]. Although agents such as mirtazapine, mefloquine, cytarabine, and cidofovir have been explored, clinical results have been disappointing. For HIV-associated PML, cART remains the cornerstone of treatment. In cases of natalizumab-related PML, treatment involves discontinuing the drug to allow for immune reconstitution. Furthermore, Granulocyte Colony-Stimulating Factor (G-CSF) may represent a novel strategy to treat natalizumab-associated PML by enhancing T-cells migration into the central nervous system (CNS) and increasing absolute lymphocyte counts[2,10]. In a retrospective study, 100% two-year survival was achieved in seventeen patients with natalizumab-related PML treated with G-CSF[10]. Immune check point inhibitors (ICIs), such as pembrolizumab and nivolumab, and interleukins (interleukin-2 and recombinant human interleukin-7) have been used to treat PML with varying degrees of success[11]. Although a few patients with HIV have received ICIs as adjunctive treatment, the outcomes remain inconclusive[12]. To date, no prospective studies of ICIs for PML in HIV patients have been conducted to consolidate this treatment strategy. The new gene-editing technique, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/ CRISPR-associated protein 9 (Cas9), has been applied to JCV. By precisely deleting specific viral genes, it can prevent viral replication and interrupt the viral life cycle[13]. Following cART initiation, PML-related IRIS must be closely monitored to optimize the treatment response[9]. MRI contrast enhancement is a valuable tool for evaluating PML-IRIS; when it occurs, patchy or punctate contrast enhancement at the lesion border on post-contrast T1-weighted images is typically noted by edema and mass effect[4,6]. In one review, IRIS developed in 4-22% of individuals with HIV-related PML and was associated with a mortality rate of 5-28%[14]. In another retrospective cohort in Brazil, most PML-IRIS cases were unmasking IRIS, occurring at a median of 49 days after starting cART[15]. Steroids remain the mainstay for IRIS treatment; additionally, C-C chemokine receptor type 5 (CCR5) antagonists (maraviroc), tumor necrosis factor-α(TNF-α) antagonists, and montelukast (a leukotriene receptor antagonist) have also been used[2,5]. The prognosis of PML in the pre-cART era was poor, with a median survival of 6 months, and only 9% of patients survived for more than 1 year[16]. In the cART era, the prognosis has improved. Individuals with HIV-associated PML have mortality rates of up to 30% at one year and 50-60% at two years[14]. In a 25-year retrospective cohort, the 10-year survival rate reached 22%[17].

The patient suffered from breakthrough high fever on day 3 of admission. Blood culture revealed concomitant MSSA and *Acinetobacter baumannii* bacteremia. Fever subsided 2 days later after initiating sulfamethoxazole/trimethoprim, to which both pathogens were susceptible according to drug susceptibility tests. Therefore, the medication was continued to complete the treatment course for bacteremia. No skin infection or distant metastatic foci were found, and no central venous catheter was used. Echocardiogram did not reveal any vegetation; thus, primary bacteremia was diagnosed. As *Staphylococcus aureus* is a common skin pathogen and *Acinetobacter baumannii* is prevalent in soil and hospital environment, the primary bacteremia was attributed to a healthcare-associated bloodstream infection (HABSI). The importance of adequate skin hygiene, environmental disinfection and infection control measures cannot be overstated.

In patients with advanced acquired immunodeficiency syndrome (AIDS), differential diagnosis of cerebral lesions is crucial. Since the patient's *Toxoplasma gondii* IgG was negative, cerebral toxoplasmosis was excluded. CMV ventriculitis typically manifests as periventricular enhancement on MRI, which was not observed. Although HIV encephalopathy could not be ruled out as CSF HIV PCR was not performed, the patient had a definite PML diagnosis and responded well to treatment; thus, no invasive procedures (e.g., biopsy for primary CNS lymphoma) were conducted. The patient's CSF showed no pleocytosis, and the protein level was only slightly above the upper limit of normal. CSF VDRL was negative, making neurosyphilis less likely, though it could not be entirely excluded. Initial brain CT findings suggesting a stroke in an HIV-infected patient should raise suspicion of neurosyphilis. Chen et al. previously reported a case of an HIV-infected patient diagnosed with neurosyphilis following repeated episodes of stroke, who was successfully treated with ceftriaxone[18]. Although the patient was ultimately diagnosed with PML, a thorough investigation in such far-advanced immunocompromised patients is indicated to exclude any possible co-infection.

In conclusion, PML is a critical disease entity among HIV-infected patients with AIDS. Early diagnosis of HIV and prompt initiation of cART may prevent this devastating disease. Reinforcing infection control measures is mandatory, especially when caring for the immunocompromised patients. Hospital-based HIV case managers, social workers and social safety net are vital for HIV patients with poor adherence or low socioeconomic status.

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進行性多發性白質腦病變合併鮑氏不動桿菌菌血症發生在一位愛滋病人身上—病例報告及文獻回顧

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摘要

進行性多發性白質腦病變是一種罕見的疾病。它大部分發生在人類免疫缺乏病毒感染者身上。如果沒有及時診斷，結果往往是災難性的。在雞尾酒療法的時代，病例數在下降。在少數社經地位不佳，無法規則回診的病人會導致愛滋病進展及增加罹患此病的風險。在這裡，我們將呈現這樣一位上述處境的病人，他一開始以肢體無力還有認知功能變差來表現。最終以典型的核磁共振腦影像及腦脊髓液經由 PCR 方法確認 JC 病毒而得到診斷。此外，他還同時罹患鮑氏不動桿菌及金黃色葡萄球菌菌血症。診斷後病人隨即接受雞尾酒療法及抗生素治療。幸運的是，沒有發生免疫重建症候群。最終，病人存活了下來，運動功能也從最早的爬著求救進步到可以拿助行器走路。