

LEFLUNOMIDE-ASSOCIATED FATAL CRYPTOCOCCAL MENINGOENCEPHALITIS PRESENTING AS RAPIDLY PROGRESSIVE DEMENTIA: A CASE REPORT

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ABSTRACT – Background: Cryptococcal meningoencephalitis is a serious opportunistic infection, classically associated with advanced immunosuppression. The increasing use of immunomodulatory drugs, such as leflunomide, has broadened the at-risk population.

Case Report: A 66-year-old woman with rheumatoid arthritis, on long-term leflunomide therapy, presented with progressive cognitive decline, behavioral changes, and myoclonus over a six-week period. The initial presentation mimicked rapidly progressive dementia. Cerebrospinal fluid analysis showed elevated opening pressure, hypoglycorrhachia, and hyperproteinorrhachia. India ink staining and culture confirmed *Cryptococcus* spp., which polymerase chain reaction (PCR) identified as *Cryptococcus gattii*. Despite antifungal treatment with liposomal amphotericin B and fluconazole, her condition deteriorated, leading to persistent intracranial hypertension, secondary infections, and multiorgan failure, resulting in death.

Conclusions: This case highlights the diagnostic challenges of cryptococcal meningoencephalitis with atypical neurological presentation and its potential association with leflunomide-induced immunosuppression. Early clinical suspicion and a multimodal diagnostic approach are essential for improving prognosis.

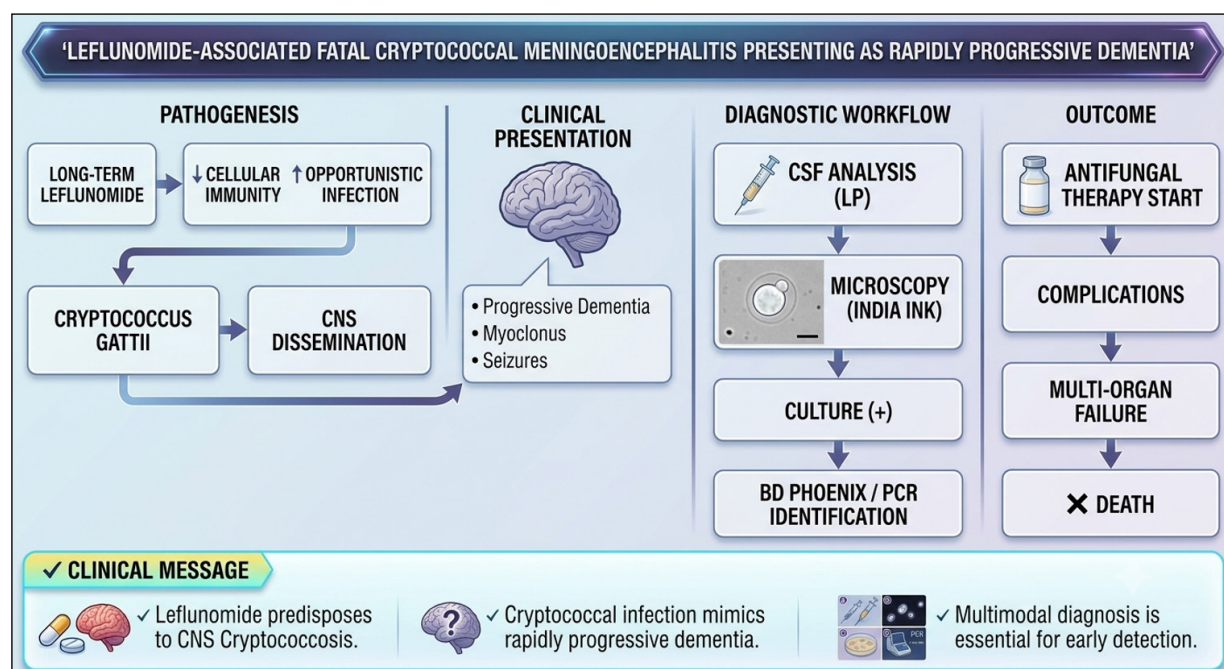
KEYWORDS: *Cryptococcus*, Leflunomide, Immunosuppression.

INTRODUCTION

Fungal infections are most commonly associated with superficial diseases such as oral candidiasis and dermatophytic skin and nail infections; however, under conditions of impaired host immunity, fungi may cause invasive and life-threatening disease. Among these, *Cryptococcus* species represent a leading cause of meningoencephalitis worldwide, particularly in immunocompromised populations¹. The HIV epidemic fundamentally reshaped the epidemiology of cryptococcal disease, establishing profound cellular immunodeficiency as a key risk factor for central nervous system

involvement. In recent years, a similar paradigm shift has emerged with the expanding use of immunomodulatory therapies for autoimmune diseases. Sustained inhibition of lymphocyte proliferation — especially T-cell-mediated immunity — has created new at-risk populations in whom opportunistic fungal infections may occur despite the absence of classical immunodeficiency².

Leflunomide, a pyrimidine synthesis inhibitor widely used in the treatment of rheumatoid arthritis, exerts long-lasting immunosuppressive effects through suppression of activated lymphocyte proliferation. Although generally considered a moderate immunomodulator, its



Graphical Abstract. Summary of the clinical presentation, diagnostic workflow, and outcome of a fatal leflunomide-associated *Cryptococcus gattii* meningoencephalitis presenting as rapidly progressive dementia.

prolonged half-life and cumulative immune effects may predispose susceptible individuals to severe opportunistic infections³. Cryptococcal meningoencephalitis may present with subacute cognitive and behavioral changes, seizures, and altered consciousness, frequently mimicking rapidly progressive neurodegenerative or prion-related disorders. Neuroimaging findings are often nonspecific in early stages, further complicating timely diagnosis. To date, cryptococcal meningoencephalitis associated with leflunomide therapy has been rarely reported. Here, we present a fatal case of cryptococcal meningoencephalitis in a patient receiving long-term leflunomide treatment for rheumatoid arthritis, highlighting the neurological presentation, diagnostic challenges, and the potential role of drug-induced immunosuppression in disease pathogenesis.

CASE PRESENTATION

A 66-year-old woman with a history of rheumatoid arthritis, hypertension, and hypothyroidism was admitted with a 6-week history of progressive cognitive impairment, behavioral changes, myoclonic jerks, and episodic loss of consciousness. The patient was on leflunomide therapy for at least 6 months; no other immunosuppressive treatment was taken during this period. Neurological examination revealed severe disorientation, poor cooperation, and pyramidal signs. Brain

magnetic resonance imaging (MRI) demonstrated diffuse cerebral and cerebellar atrophy with subsequent development of hydrocephalus and periventricular white matter changes. Given the rapid neurological deterioration and decline in O₂ saturation, the patient was intubated, and a lumbar puncture was performed. Cerebrospinal fluid (CSF) opening pressure was markedly elevated (320 mmH₂O). Biochemical analysis showed severe hypoglycorrhachia (15 mg/dL) and extremely elevated protein levels (989 mg/dL), with lymphocytic predominance.

The patient was receiving prednisolone 1,000 mg, ceftriaxone 2*1, vancomycin 2*1, levothyroxine 100 mcg, carvedilol 6.25, benipin hydrochloride 8 mg, candesartan 16 mg, aspirin 100 mg, and indomethacin 25 mg when hospitalized. On day 4, due to clues of CSF, the patient was thought to have fungal meningitis; prednisolone was dropped to 500 mg/day, liposomal amphotericin B 4 mg/kg, and fluconazole 600 mg were started.

Microbiological findings

Direct Gram staining of CSF demonstrated rare polymorphonuclear leukocytes and yeast cells. Indian ink staining of CSF showed yeast cells (Figure 1), and CSF culture yielded *Cryptococcus* spp., which was identified by the BD Phoenix™ Automated Microbiology System (BD Diagnostics, Sparks, MD, USA). The multiplex meningitis poly-

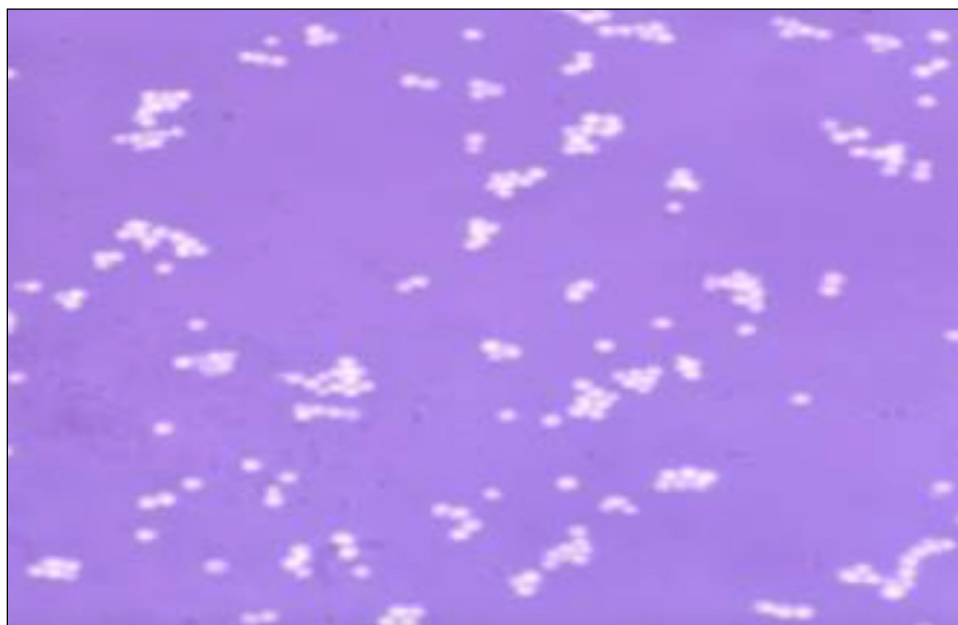


Figure 1. Microscopic image of *Cryptococcus* in the laboratory (1,000 $\times$).

merase chain reaction (PCR) panel was initially negative but later positive for *Cryptococcus gattii* on repeat testing. John Cunningham virus (JCV) and BK virus PCR assays in blood and CSF were negative. The CSF 14-3-3 protein and RT-quick test for prion disease were negative.

Treatment and outcome

Repeated lumbar puncture showed persistent elevated opening pressure and ongoing inflammatory findings, though partial biochemical improvement was observed following antifungal therapy. Induction antifungal therapy was initiated with liposomal amphotericin B (4 mg/kg/day) and high-dose fluconazole. Corticosteroids were administered intermittently due to cerebral edema and elevated intracranial pressure. The clinical course was complicated by hepatotoxicity, nephrotoxicity, aspiration pneumonia, secondary bloodstream infection (*Enterococcus faecalis*), and acute respiratory failure requiring mechanical ventilation. Despite sustained antifungal treatment and supportive intensive care, the patient developed multiorgan failure and died on hospital day 38 following refractory cardiac arrest.

Early in the disease course, the patient was evaluated with several clinical possibilities. However, JC-BK virus PCR for suspected progressive multifocal leukoencephalopathy (PML) and CSF 14-3-3 protein and RT quick for PrP for prion diseases were negative. Corticosteroids were administered intermittently due to cerebral edema and elevated intracranial pressure. As in previous

studies⁴, pulse corticosteroid therapy paradoxically temporarily lowered acute-phase reactants and improved the patient's clinical state. This emphasizes the central effects of infection. Following positive diagnostic tests for *Cryptococcus* spp., the patient was diagnosed with chronic meningoencephalitis. In culture-based diagnostic approaches, a high infectious burden may result in detectable growth within three to four days. Most infections usually grow within seven days⁵. CSF culture sensitivity depends heavily on the volume of fluid sampled. Quantitative culture allows estimation of fungal burden in CFU per milliliter, with excellent sensitivity at high organism loads (>100,000 CFU/mL) but a markedly increased risk of false-negative results at low burdens. From the beginning to the end of hospitalization, the patient's immature granulocyte values were higher at $0.80 \times 10^9/L$, indicating infection, inflammation, or bone marrow disorder. The failure to perform a rapid *Cryptococcus* antigen test here is a shortcoming.

DISCUSSION

Leflunomide is an immunomodulatory agent that exerts its primary action through the active metabolite A77 1726, which inhibits dihydroorotate dehydrogenase (DHODH), a key enzyme in *de novo* pyrimidine synthesis. Because activated lymphocytes rely heavily on *de novo* synthesis to proliferate, leflunomide preferentially suppresses T-cell expansion, IL-2-dependent proliferation, and Th1-mediated immune responses⁶.

Protective immunity against *Cryptococcus* species—which are ubiquitous environmental fungi transmitted exclusively *via* inhalation of airborne cells—depends fundamentally on cellular immune mechanisms. Specifically, CD4+ T-helper 1 (Th1) responses and interferon gamma (IFN- γ) production are critical for robust macrophage activation, phagocytosis, and fungal clearance. By interrupting lymphocyte proliferation and Th1 cytokine signaling, long-term leflunomide therapy creates a state of selective cellular immunodeficiency. Although often categorized as a moderate immunosuppressive agent compared with anti-TNF therapies or high-dose calcineurin inhibitors, cumulative leflunomide exposure can impair macrophage activation and compromise host defenses against opportunistic fungal pathogens⁷.

In our case, the patient presented with sub-acute, progressive cognitive decline and neuro-behavioral changes mimicking prion-like or rapid neurodegenerative disorders. Initial diagnostic challenges were compounded by negative early PCR testing, underscoring that a single negative molecular assay during initial evaluation does not rule out fungal infection. Subsequent CSF analysis, Indian ink staining, and automated identification confirmed *Cryptococcus gattii*. The sensitivity of CSF culture for *Cryptococcus* is heavily contingent upon sampled fluid volume and fungal load. The diagnostic sensitivity of CSF culture is closely influenced by the fungal burden, with low organism loads being associated with a higher risk of false-negative results. Importantly, increasing the volume of CSF subjected to culture can improve the detection of low-level cryptococcal infection. Furthermore, the absence of a rapid cryptococcal antigen test (CrAg) during the initial diagnostic workup is a notable limitation in this case; CrAg remains the gold standard for rapid screening because of its superior sensitivity and specificity⁸.

Recent data⁹ have directly demonstrated the concurrent bifunctionality of leflunomide as both immunosuppressive and antiviral in an allogeneic cardiac transplant model of rat cytomegalovirus (RCMV) infection, with a serum dose of 100 $\mu\text{g}/\text{mL}$ resulting in serum A77 1726 levels of $\sim 100 \mu\text{g}/\text{mL}$ or 300 μM as a pharmacokinetic product. Leflunomide's antimicrobial effect has also been studied against rotavirus, *Helicobacter pylori*, *Plasmodium falciparum*, and *Schistosoma mansoni*¹⁰. Further research may help elucidate the drug's mechanism of action.

CONCLUSIONS

Cryptococcal meningoencephalitis may present as rapidly progressive dementia with prominent cognitive and behavioral symptoms, closely mimicking neurodegenerative or prion-related disorders. Le-

flunomide-associated immunosuppression, despite being often perceived as moderate, can predispose patients to severe opportunistic central nervous system fungal infections. Cerebrospinal fluid culture sensitivity depends strongly on CSF volume and fungal burden; low organism loads may cause false-negative cultures. Early PCR negativity during induction therapy does not indicate microbiological cure and should not be used as a standalone marker of treatment response. Positive CSF 14-3-3 protein reflects nonspecific neuronal injury and should be interpreted with caution in infectious encephalitis. A multimodal diagnostic approach integrating clinical features, serial CSF analyses, culture, antigen testing, and neuroimaging is essential for accurate diagnosis.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

FUNDING

This study received no external funding.

ETHICS APPROVAL

Ethics Committee approval was not required for this case report.

INFORMED CONSENT

Written informed consent for publication was obtained from the patient's legal representative.

DATA AVAILABILITY

All relevant data are included in the manuscript.

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AUTHORS' CONTRIBUTIONS

Methodology: SAK, FK; Software: SAK; Validation: SAK; Formal analysis: FK; Investigation: SAK, FK, KAS; Resources: FK, KAS; Data curation: SAK, FK, KAS; Writing – original draft preparation: SAK; Writing – review and editing: SAK, FK; Visualization: SAK; Supervision: FK; Project administration: SAK; All authors have read and agreed to the published version of the manuscript.

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