

Fingolimod related cryptococcal meningitis and immune reconstitution inflammatory syndrome in two patients with multiple sclerosis

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Objective

We report two cases of fingolimod associated cryptococcal meningitis while on fingolimod and subsequent central nervous system immune reconstitution inflammatory syndrome (CNS IRIS) after drug discontinuation.

Cases Description

- Two women with fingolimod associated cryptococcal meningitis were identified, ages 40 and 48, with a mean duration of fingolimod treatment of 4.5 years.
- Both patients were lymphopenic at presentation (mean nadir of 207/ μ L).
- They presented with headache, fever, and altered mental status.
- Their MRIs had leptomeningeal enhancement. Spinal fluid analysis was notable for marked neutrophilic pleocytosis and elevated protein.
- Cryptococcus meningitis was diagnosed based on antigen detection by latex agglutination in CSF and serum, as well as positive CSF culture.
- Both patients required a ventriculoperitoneal shunt for persistent elevation of intracranial pressure.
- They had clinical and radiological deterioration at mean 101 +/- 25 days after discontinuation of fingolimod despite continuing on antifungal therapy.
- They were diagnosed with CNS IRIS and had some improvement with steroids.

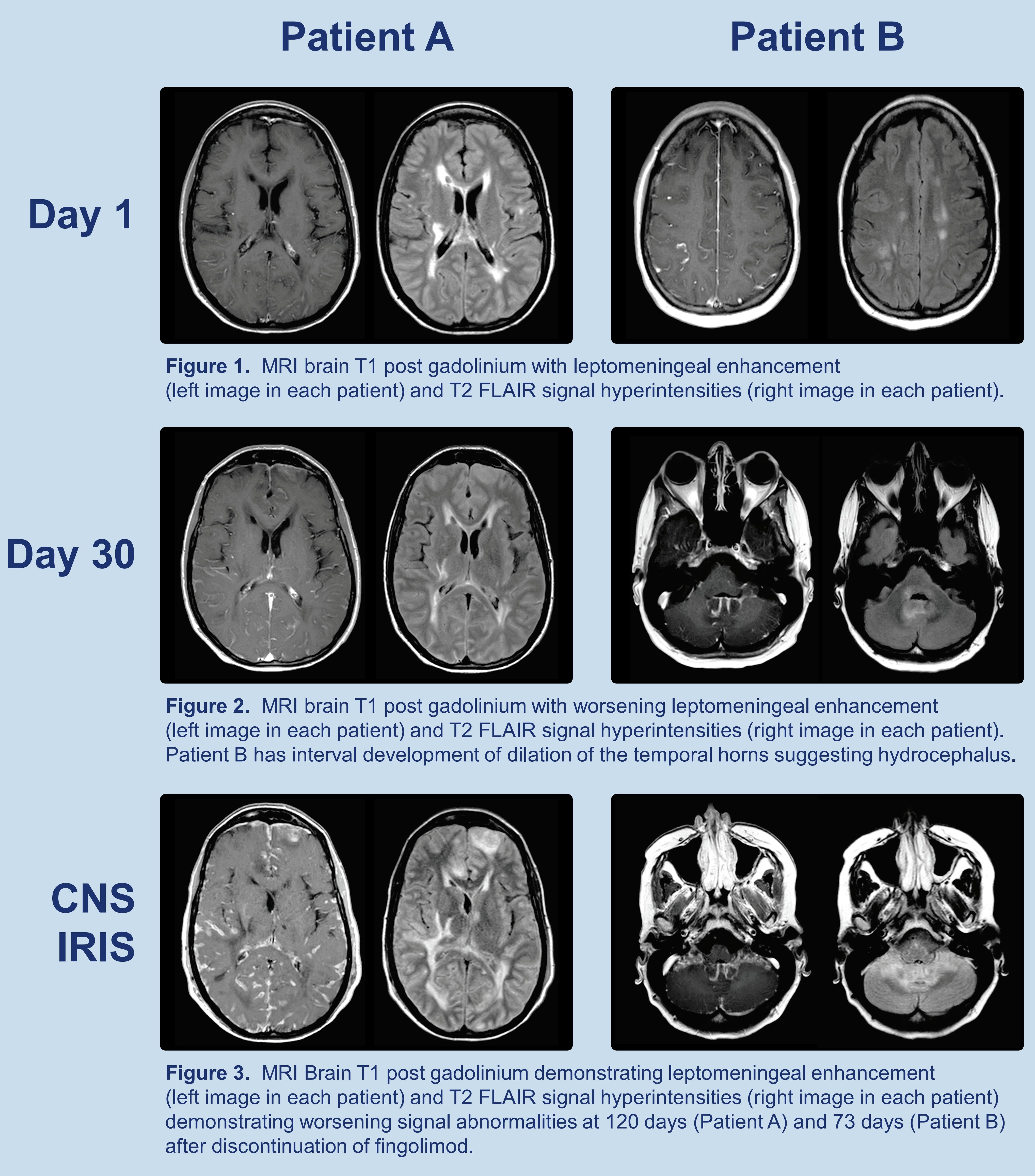


Table 1. CSF Findings	Patient A			Patient B		
	Day 1	Day 30	CNS IRIS	Day 1	Day 30	CNS IRIS
Opening Pressure (5-18 cm H2O)	52	30	60	>55	33	10
WBC Count (<5/ μ L)	22	45	39	99	10	76
Neutrophils (%)	7	4	53	64	0	13
Lymphocytes (%)	35	80	40	6	89	76
Mono (%)	55	16	6	30	11	11
Glucose (30-73 mg/dL)	7	8	26	15	22	24
Protein (15-45 mg/dL)	142	204	864	76	112	393
Cryptococcal Antigen (Titer)	Positive (1:512)	Positive (1:32)	Positive (1:8)	Positive (1:1024)	Positive (1:16)	Positive (1:64)
Cryptococcal Culture	Positive	Negative	Negative	Positive	Negative	Negative

Discussion

- Drug-induced lymphopenia and persistent headache were red flags that prompted a spinal tap and testing for opportunistic infections.
- Risk may be higher with longer durations of therapy, older age and lymphopenia.
- Prognosis is poor, and clinical deterioration should be closely monitored for relapsing infection, hydrocephalus, or CNS IRIS.
- Prompt lumbar puncture for atypical symptoms, serum cryptococcal antigen screening, and CD4 monitoring may be needed for earlier identification.
- Discontinuation of fingolimod has led to CNS IRIS.
- The need for cryptococcal antigen surveillance pre-therapy and possibly yearly while on therapy may become important in predicting the risk of infection in the older population.

Selected References

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- Achtnichts L, Obreja O, Conen A, Fux CA, Nedeltchev K. Cryptococcal meningoencephalitis in a patient with multiple sclerosis treated with fingolimod. *JAMA Neurology.* 2015;72(10):1203-5.

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