Successful Treatment of Refractory Disseminated Coccidiomycosis with Adjunctive Interferon-γ

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Background

Coccidiomycosis (CM) is a disease caused by the fungal pathogens *Coccidioides immitis* and *Coccidioides posadasii,* which are endemic to the southwestern United States. Most cases of CM are asymptomatic or cause mild respiratory illness. 1% of cases develop extra-pulmonary dissemination with cutaneous, skeletal, or CNS involvement, which can be serious and sometimes fatal. In cases that fail to respond to antifungal treatment regimens, immunomodulatory interventions may be required to treat infection.

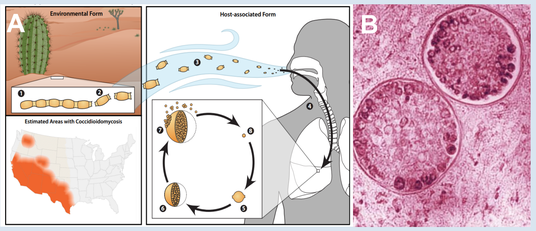


Figure 1: Biology and distribution of Coccidiomycosis. (A) *Coccidioides spp.* exist in the environment as a mold with septate hyphae. When disturbed, hyphae separate into arthroconidia and can be carried via wind and travel into the respiratory system. Once in a human host, hyphae form spherule structures (B), which are filled with endospores. As spherules rupture, endospores are released into additional tissues.

Case Description

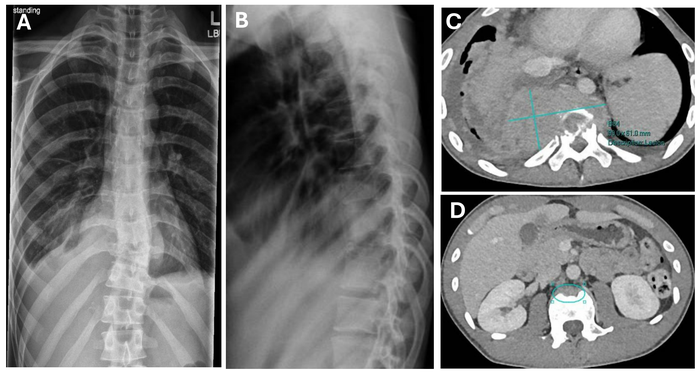
A previously healthy 19-year-old African American male was referred to the NIH with refractory disseminated coccidioidomycosis (DCM) complicated by a paraspinal phlegmon and a T10 compression fracture. The infection had failed to respond to three weeks of dual antifungal therapy with itraconazole and amphotericin B. The patient reported living in Arizona for 12 months approximately 2 years prior to presentation.

On presentation, he exhibited severe disseminated infection involving the lungs and pleural space, lytic lesions in multiple thoracic vertebrae, and a pathologic fracture at T10. Lung biopsies and serum testing confirmed coccidioidomycosis without evidence of secondary infection.

Upon admission, antifungal therapy with amphotericin B, caspofungin, and posaconazole was initiated; however, his symptoms continued to worsen. Due to poor tolerance of amphotericin B, adjunctive interferon-gamma (IFN-γ) therapy (50 mcg/m^2, administered subcutaneously 3 times per week) was added alongside continued posaconazole treatment.

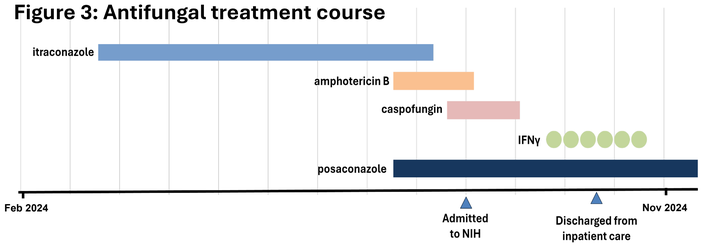
Clinical Course

Figure 2: Radiology images demonstrating disease severity upon admission to NIH



(A-B) Radiographs showing right lower chest pleural effusion and a paraspinal mass. Acute focal kyphosis at to T10 due to markedly compressed T10 vertebra with adjacent T9 and T11 vertebral body sclerotic changes. **(C)** Radiograph showing total compression of T10 with large soft tissue lesions, measuring 99 x 61mm (measured in blue), with soft tissue extending to the anterior epidural space and neural foramina. **(D)** Radiograph showing multiple soft tissue nodules and fluid with extension of fluid and soft tissue into the right major fissure.

Figure 3: Antifungal treatment course



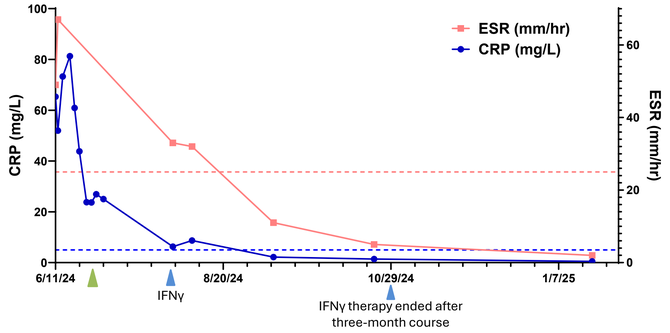
Antifungal interventions administered at a referring hospital and at NIH between February 2024 and November 2025. Bars indicate the duration of each antifungal treatment; horizontal gridlines represent two-week intervals. The patient remains on posaconazole. IFN-γ) was administered subcutaneously at 50 mcg/m^2, 2–3 times per week, during inpatient and outpatient care, and continued for approximately one month following discharge.

Table 1: Whole genome sequencing results

Gene (transcript)	DNA change	Protein change	Zygosity	Classification	Associated Disease	Disease Inheritance
PLCG2 (NM_002661.5)	c.802C>T	p.Arg268Trp	Heterozygous	Risk Allele	Susceptibility to disseminated coccidioidomycosis	Autosomal dominant

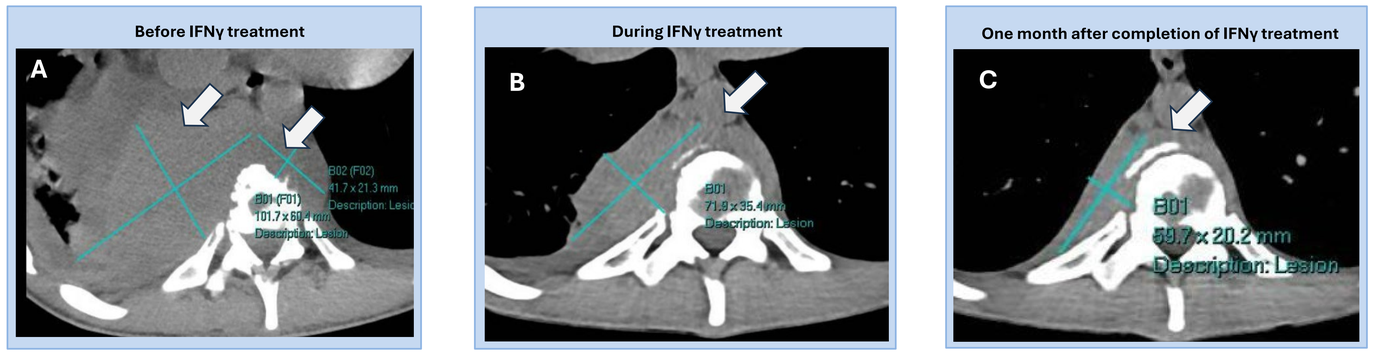
The p.Arg268Trp variant in *PLCγ2* has been identified as a putative risk allele associated with susceptibility to disseminated coccidioidomycosis (DCM) following primary infection. This variant is present at an allele frequency of 4.6% in the gnomAD database. Based on current evidence, including findings reported in PMID: 38054408, the p.Arg268Trp variant is classified as a risk allele of uncertain significance.

Figure 4: Inflammatory markers over treatment course



Improvement of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) over treatment course at NIH. Pink dashed line marks the upper limit of normal ESR (25 mm/hr). Blue dashed line marks the upper limit of normal CRP (5 mg/L). The patient's CRP peaked at 81.3mg/L in June 2024, while being treated with amphotericin B, caspofungin and posaconazole. The date in which amphotericin B was discontinued is marked by the green arrow. CRP levels fell into normal ranges after approximately one month of subcutaneous IFNγ treatment. ESR rates similarly improved, becoming normal after the addition of IFNγ .

Figure 5: CT scans of patient showing improvement in soft tissue lesions before, during, and after IFNγ therapy



Sequential radiograph images show improvement in soft tissue lesions (arrows) over the course of IFNγ treatment, left to right. A) Initial chest radiograph showing a large prevertebral and paraspinal mass adjacent to T10 (left arrow; 102 × 60 mm) and a smaller lesion (right arrow; 42 × 21 mm). (B) Radiograph approximately one month after initiation of IFNγ treatment, showing decreased size of the primary mass (72 × 35 mm). (C) Final radiograph one month after the completion of treatment demonstrating continued reduction in mass (60 × 20 mm).

Outcome

The patient's condition improved rapidly after the addition of IFNγ with resolution of severe pain and normalization of C-reactive protein (CRP) levels (2.2 mg/L) approximately one month after starting IFN-γ therapy. A follow-up CT scan at two months demonstrated marked reduction in measurable disease.

Post-treatment whole genome sequencing identified a heterozygous R268W variant in the *PLCG2* gene. This mutation has been associated with impaired β-glucan–induced TNF-α production by PBMCs, which may cause defects in fungal sensing.

Currently, the patient remains on posaconazole monotherapy, with continued radiographic improvement and appropriate weight gain. IFN-γ therapy has been discontinued, but remains on posaconazole. The patient experiences residual paraspinal pain that is relatively well controlled with minimal pharmacologic intervention.

Discussion

This case highlights the successful use of adjunctive IFN-γ therapy in a patient with refractory DCM who failed to respond to standard antifungal regimens. Despite escalation in antifungal therapy, the infection continued to progress until the addition of IFN-γ led to measurable clinical improvement.

IFN-γ–driven immunity is critical for the control of intracellular pathogens, as evidenced by the fact that monogenic defects in IFN-γ signaling pathways cause severe mycobacterial and dimorphic fungal infections, including DCM. Treating DCM with IFNγ could be effective in enhancing immune responses in treatment-resistant cases, leading to improved clearance of refractory fungal infections when traditional treatment regimens fail to resolve infection.

References

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