

# Journal Pre-proof

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# Refractory Thoracic Conidiobolomycosis Treated With Mepolizumab Immunotherapy

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## 48    **Clinical Implications**

49    We describe the first use of mepolizumab immunotherapy for invasive fungal infection in a  
50    child with life-threatening thoracic conidiobolomycosis. This novel approach demonstrates  
51    the potential utility of immunomodulatory therapies in infections associated with an aberrant  
52    Th2 response and eosinophilic inflammation.

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Immunotherapy is an emerging approach to the treatment of invasive fungal infections, made possible by improved understanding of host-pathogen interactions and novel targeted therapeutic agents.(1, 2) Here, we report a case of life-threatening thoracic conidiobolomycosis where introduction of the anti-IL5 monoclonal antibody mepolizumab was decisive in achieving cure.

A previously well 6-year-old boy with protracted cough, fever and weight loss was eventually diagnosed with thoracic conidiobolomycosis. He had migrated from South East Asia 12 months prior to presentation. There was no history of recurrent infections or atopy. Initial blood tests showed leukocytosis with eosinophilia (790 cells/uL). Fluorodeoxyglucose-positron emission tomography/magnetic resonance imaging (FDG-PET/MRI) on day 11 showed an isolated avid right mediastinal mass (Figure 1).

An open biopsy was undertaken on day 19 following an acute respiratory deterioration necessitating intubation, with progressive obstruction evident on imaging. Histopathology demonstrated eosinophil-rich granulomatous inflammation (Figure E1). Fungal hyphae were seen on direct microscopy and *Conidiobolus incongruus* was cultured (Figure E1).

Liposomal amphotericin B was started, with dexamethasone (0.3 mg/kg/day IV) for critical airway obstruction. Antifungal susceptibility testing showed resistance to all triazoles and echinocandins. Amphotericin susceptibility was intermediate (minimum inhibitory concentration (MIC) 4 mg/L). Terbinafine disk-diffusion indicated susceptibility with a 35 mm zone of inhibition. Terbinafine was subsequently added. Dexamethasone was ceased on day 24 after resolution of fever and extubation.

On day 33, fever and respiratory distress returned, with new hemoptysis, peripheral blood eosinophilia (1160 cells/uL), and radiological progression of the mass. Dexamethasone was restarted (0.3 mg/kg/day IV) and miltefosine added to the antifungal regimen based on

evidence of in vitro activity (MIC 4ug/mL). Airway obstruction, fever, and peripheral eosinophilia resolved over 4 days.

An underlying immunodeficiency was not identified by: measurement of lymphocyte subsets including Th17; immunoglobulins A, G, and M; neutrophil oxidative burst; STAT1 and STAT4 phosphorylation; CD18 expression; and lymphocyte proliferation studies (Table E1). Immunoglobulin E (IgE) was elevated at 1123 kU/L (day 34). Serological tests for HIV, hepatitis B and hepatitis C were negative.

He remained stable on antifungal therapy and oral prednisolone (2 mg/kg/day). Repeat FDG-PET/MRI (day 81) showed mild reduction in the size and avidity of the mass. IgE remained elevated at 451 kU/L (day 83). Prednisolone was weaned over 6 weeks (to 0.5 mg/kg/day). While asymptomatic, repeat imaging (day 135) showed slight increase in size and avidity (Figure 1). Prednisolone was increased again (2mg/kg/day).

Hyperbaric oxygen therapy (from day 153) and mepolizumab (5mg/kg subcutaneously monthly from day 193) were commenced sequentially. Prednisolone was reduced gradually following initiation of mepolizumab (Table E1). He remained clinically well with a low peripheral eosinophil count. Repeat FDG-PET/MRI on day 256 showed marked reduction in the size and metabolic activity at the site of infection with complete radiological resolution by day 375 (Figure 1). Seven monthly doses of mepolizumab were given in total, the last on day 366. Antifungal therapy was stopped on day 376. At 12-months follow-up, the patient was well with no clinical, hematological, biochemical, or radiological evidence of relapse.

Conidiobolomycosis is an endemic fungal infection of the tropics and subtropics caused by *Conidiobolus* spp. including *Conidiobolus incongruus*.(3, 4) The typical presentation is of

painless, progressive rhinofacial swelling in previously healthy young adults following inhalation of fungal spores(3). Isolated cases of invasive infection with *Conidiobolus* spp. involving the lower respiratory tract and mediastinum have been described in immunocompromised and immunocompetent patients.(3) Antifungal therapy for conidiobolomycosis is often ineffective with *in vitro* resistance to most available agents; clinical outcomes have been described as ‘disappointingly variable’.(4) Mortality in reported cases of invasive conidiobolomycosis exceeds 50%.(3)

Histopathological examination of tissue infected with *Conidiobolus* spp. typically shows dense eosinophil-rich inflammation surrounding fungal hyphae (Splendore-Hoepli phenomenon).(3, 4) Together with peripheral blood eosinophilia, this is indicative of a Th2 host immune response triggered by *Conidiobolus* spp. which encapsulates the invading fungus in an inflammatory granuloma.(3) The fungal hyphae are only partially contained in the granulomata rather than eliminated, with slow progression of infection.(3) It is postulated that *Conidiobolus* and other pathogens trigger this host immune response as an evolutionary strategy to shield critical antigens from host immune effector responses (Figure 2).(3) Although no immunodeficiency was identified in this case, we postulate that an aberrant Th2-driven immune response favored progression of disease prior to initiation of corticosteroids.

High-dose corticosteroids increase susceptibility to fungal infections through broad impairment of innate and adaptive immune defenses, particularly Th1 and Th17 cellular responses central to clearance of fungal infection.(5) In our patient, high-dose steroid treatment, commenced initially for the management of critical airway compression, rapidly achieved symptomatic control, reduced the size of the mediastinal mass, and suppressed peripheral blood eosinophilia. However, prior to initiation of mepolizumab, rebound clinical and radiological progression occurred with each attempt to reduce the prednisolone dose below 2 mg/kg/day. We hypothesize that this partial response to corticosteroids was mediated

by suppression of Th2 driven eosinophilic inflammation on one hand, counterbalanced by suppression of innate and Th1 and Th17 adaptive immune effector responses on the other, resulting in failure to clear the infection (Figure 2). In contrast to reports of disseminated conidiobolomycosis where eosinophilic inflammation was absent, high-dose corticosteroid treatment in our patient did not lead to disseminated disease, possibly due to concomitant antifungal therapy and the absence of identifiable underlying immunodeficiency based on functional testing.

Mepolizumab is a monoclonal antibody against interleukin-5 (IL-5), the cytokine which drives recruitment, proliferation and maturation of eosinophils.(6) Eosinophils are a major Th2 effector cell, producing allergic inflammation, tissue damage, and fibrosis.(7) Mepolizumab is effective in conditions characterized by eosinophilic inflammation, including hypereosinophilic syndromes, eosinophilic asthma, and eosinophilic granulomatosis with polyangiitis.(6)

After mepolizumab was started for our patient there was a marked radiological response without relapse as corticosteroids were weaned (Figure 1). We postulate that IL-5 blockade inhibited eosinophil recruitment and degranulation, disrupting the granulomatous eosinophilic inflammation encasing the invading *Conidiobolus* hyphae, exposing the fungus to antifungal drug therapy and effective host immune responses freed from the suppressive action of high-dose corticosteroids (Figure 2). It is also plausible that reduced production of Th2-type cytokines (IL-4, IL-5 and IL-13) by eosinophils may have also allowed for a more appropriate Th1/Th17 response. Notably, there is evidence from animal models of chronic parasitic infection that host eosinophilic response may in fact facilitate sustained infection with the removal of eosinophils resulting in parasite elimination(8).

Although there are no previous reports of anti-IL-5 therapy in invasive mycoses, there is emerging evidence that mepolizumab is effective in allergic bronchopulmonary aspergillosis, a condition characterized by a marked Th2 immune response.(9) Successful treatment of disseminated coccidioidomycosis including immunotherapy targeting the Th2 cytokines IL-4 and IL-13 has also been reported recently.(2)

In summary, this is the first description of mepolizumab immunotherapy as part of the multimodal curative therapy of invasive conidiobolomycosis, an infection which is poorly responsive to conventional therapies. Targeted immunotherapy warrants further investigation for use in infections caused by *Conidiobolus* spp. and other pathogens causing infections associated with a maladaptive host immune response.

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Figure 1: Treatment and radiological progression on serial Fluorodeoxyglucose-positron emission tomography/magnetic resonance imaging (FDG-PET/MRI) of mediastinal conidiobolomycosis

Figure 2: Overview of Host Immune Responses to *Conidiobolus* and Proposed Effect of Corticosteroids and Mepolizumab

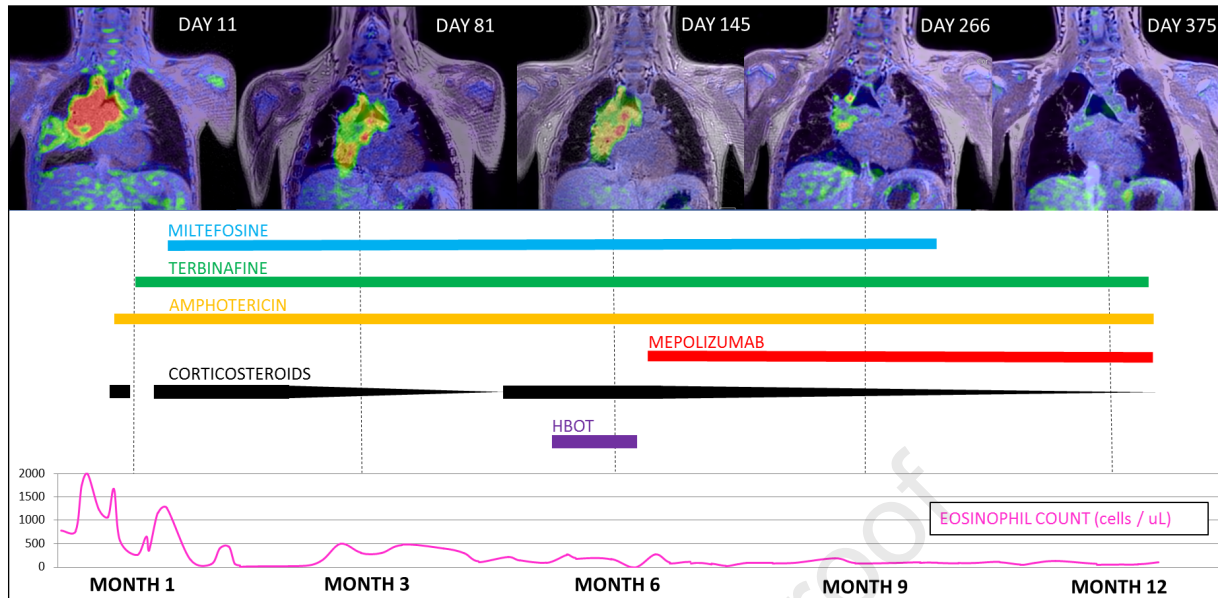
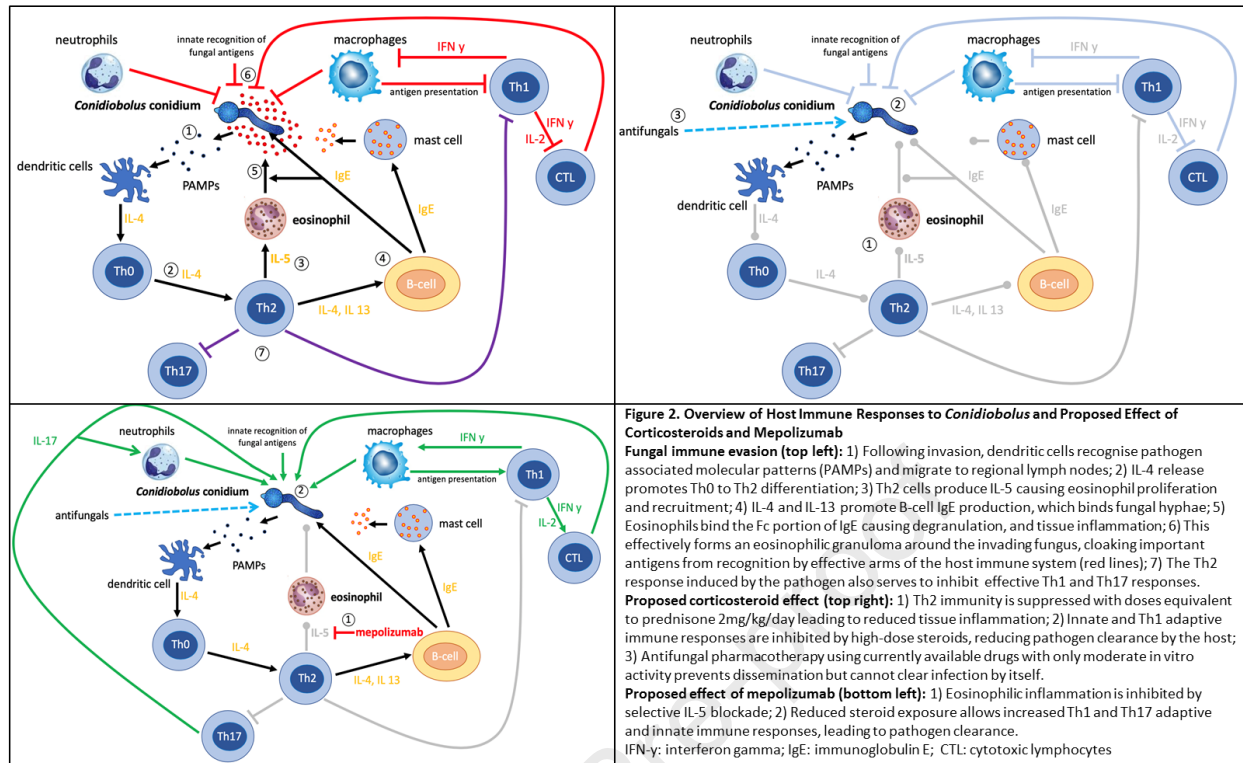


**Figure 1. Treatment and radiological progress on serial Fluorodeoxyglucose-positron emission tomography/magnetic resonance imaging (FDG-PET/MRI) of mediastinal conidiobolomycosis**  
Initial FDG-PET/MRI on day 11 of admission shows an intensely FDG avid right hilar and mediastinal mass. Corticosteroids are commenced for progressive airways obstruction on day 19. Concurrently liposomal amphotericin is started following diagnostic biopsy of the mediastinum, followed by terbinafine on day 23: fever and symptoms of obstruction resolve. On day 30 miltefosine is added and steroids are re-started following further clinical deterioration. Corticosteroids are weaned from day 81 after repeat FDG-PET/MRI shows mild reduction in size and avidity of the mass. Corticosteroids are again increased (prednisolone 2mg/kg/day) on day 135 after repeat FDG-PET/MRI showed a slight increase in size and avidity of the mass. Hyperbaric oxygen therapy (HBOT) is subsequently commenced on day 153 followed by mepolizumab on day 193 with concurrent weaning of corticosteroids. FDG-PET/MRI on day 256 demonstrates marked improvement with complete resolution by day 375. Reduction of peripheral eosinophil count was observed with high dose corticosteroids initially and subsequently following initiation of mepolizumab therapy. Miltefosine: 30 mg/day twice daily; Terbinafine: 125mg twice daily; Liposomal amphotericin: 5.0-7.5mg/kg daily



## Repository Figure Legend

Figure E1: Initial diagnostic investigations mediastinal conidiobolomycosis

Left – Histopathology of mediastinal biopsy showing islands of radiating eosinophilic inflammation surrounding fungal hyphae; the Splendore Hoespli phenomenon (arrows), bar is 50µm.

Right – *Conidiobolus incongruus* conidia with multiple coenocytic hyphae on light microscopy from mediastinal biopsy, bar is 20µm (day 23)

