Published in final edited form as:

Pediatr Transplant. 2018 December ; 22(8): e13294. doi:10.1111/petr.13294.

Necrotizing fasciitis caused by *Mucor indicus* in a pediatric bone marrow transplant recipient

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Abstract

Necrotizing fasciitis is a life-threatening, rapidly progressing infection of fascia and subcutaneous cellular tissue typically caused by mixed aerobic and anaerobic bacteria. We present a case report of an immunocompromised 4-year-old female with necrotizing fasciitis from a rare fungal organism, *Mucor indicus*. The patient underwent multiple debridements and was treated for 10 months, first on liposomal amphotericin B (2 months) then posaconazole (8 months). *Mucor indicus* is a rarely described pathogen with only nine other cases described. Identification of this organism remains a challenge, and the need for further understanding of risk factors and organism susceptibility testing to help guide treatment is crucial.

Keywords

bone marrow transplantation; *Mucor indicus*; *Mucorales*; necrotizing fasciitis

1 | INTRODUCTION

Necrotizing fasciitis is a life-threatening, rapidly progressing infection of fascia and subcutaneous cellular tissue typically caused by mixed aerobic and anaerobic bacteria. The estimated incidence of necrotizing fasciitis is 0.08 per 100 000 pediatric patients per year,^{1,2} and a mortality rate ranging from 2% to 73%.³ Only a few case reports and case series describe necrotizing fasciitis in pediatric patients with hematologic malignancies, with

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AUTHORS' CONTRIBUTIONS

All authors contributed to the writing and editing of this manuscript. Drs. Gonzalez and Abramowsky: contributed the microbiology and pathology images and their descriptions.

CONFLICTS OF INTEREST

None of the authors report any conflict of interests.

Gram-negative rods⁴ and *Clostridium perfringens*⁵ being the most commonly recovered pathogens.

In patients with immunocompromising conditions, fungi can also cause necrotizing fasciitis, specifically those belonging to the angioinvasive order, *Mucorales* (formerly *Zygomycetes*). Genera pathogenic to humans include *Rhizopus*, *Mucor*, *Lichtheimia* (formerly *Absidia*), *Rhizomucor*, *Saksenaea*, *Cunninghamella*, *Syncephalastrum*, and *Apophysomyces*.^{6,7} The *Mucorales* are pervasive in the environment, found in soil and decaying vegetation, and sporangiospores can be inhaled or ingested.⁸ With only nine other cases described in the literature, we present a case report of a 4-year-old female with high-risk pre-B-cell ALL who developed *Mucor indicus* groin necrotizing fasciitis, myositis, and cellulitis.

2 | CASE PRESENTATION

A 4-year-old female with very high-risk (near haploid) pre-B-cell ALL in first remission failed to engraft after an allogeneic partially matched related peripheral blood stem cell transplant from her haploidentical mother and underwent second transplant from her haploidentical father. She developed acute onset fever to 38.3°C (axillary) and painful groin swelling following 7 months of prolonged neutropenia and 9 days after the second transplant. There were no overlying breaks in the skin and no history of vascular catheterization or other procedures at the site of inflammation. She had been on prophylaxis with inhaled pentamidine (18 mg/kg/dose, inhaled, monthly) for *Pneumocystis jirovecii* pneumonia, and VRC (14 mg/kg/d, PO, BID) for 2 months prior to onset of symptoms. Her examination was significant for swelling over the inguinal ligaments bilaterally that were erythematous and extremely tender to the touch. Pelvic MRI revealed cellulitis and fasciitis with bilateral inguinal small abscesses, and bilateral adjacent myositis of the iliopsoas, pectineus, abductor brevis, and longus muscles (Figure 1A). No free air was visualized. The patient was empirically started on meropenem (20 mg/kg/dose, IV, every 8 hours) plus vancomycin (20 mg/kg/dose, IV, every 8 hours) and micafungin (4 mg/kg/d, IV, daily) was added to her fungal coverage. She was taken to the operating room for right groin exploration, bilateral needle aspiration of the adenopathy, and lymph node biopsy. Pathologic review showed fungal elements (Figure 1B), which prompted switching micafungin to L-AmB (5 mg/kg/d, IV, daily). At the time of the first debridement, the patient was getting human GCSF. She was also started on methylprednisolone (0.45 mg/kg/dose BID) for graft-versus-host disease. She developed neutrophil count recovery within a week after the development of the pain.

On post-operative day 2 (about 45 hours after specimen receipt), specimens obtained in the operating room yielded mold on the aerobic blood agar plate, incubated at 35°C (Figure 1C,D). There was also rare growth on the chocolate agar plate and the anaerobic blood agar plate. The mold was identified as *M. indicus* by the Centers for Disease Control and Prevention by sequencing of internal transcribed spacer regions of ribosomal deoxyribonucleic acid, as previously described by Lockhart, et al, 2013.⁹ Subsequent specimens from further debridement grew out the same pathogen on dedicated fungal media. Antifungal susceptibility testing for AmB, ITR, and VRC was done by ARUP Laboratories in Salt Lake City, Utah. Disseminated fungal disease survey with an echocardiogram,

ophthalmologic examination and maxillofacial, chest, abdomen, and pelvis CT was completed with no significant findings. She underwent three more debridements every 4 days over the next 16 days, had wound vacuums placed followed by a final washout and drain placement. The drain was removed 22 days after the initial surgery. Of the twelve tissue specimens sent for culture from bilateral sites with the second debridement, four specimens grew mold from deep sites bilaterally. Of five specimens sent with the third debridement, only one deep left sided specimen culture grew mold. No cultures were sent from the last debridement since no gross pathology was visualized within the surgical field and no fungal elements were seen on frozen section. She achieved full donor engraftment and her leukemia remained in remission on post-transplant day 17.

The patient was discharged on post-transplant day 32, on L-AmB. She was transitioned to POS 2 months later (final level-adjusted dose was 8.8 mg/kg/dose, PO, four times a day, to achieve a target level of 0.7 mg/L). On follow-up visits, she was asymptomatic and tolerating POS well. Repeat MRI of the groin showed gradually diminished inflammation until full recovery, and POS was discontinued after 10 months of total antifungal therapy. At a clinic visit on day 511 post-transplant, there was no evidence of ALL or infection recurrence.

3 | DISCUSSION

Mucor indicus was first discovered in the late 19th century and is generally considered a non-pathogenic organism. It has wide industrial application, for example, it is used in the production of ethanol and beer, and for taste in meat-substitute products like tempeh.^{6,7,10} Additionally, it is used in food fermentation of rice and manioc. *Mucor indicus* has unique fungal properties: it is able to grow in aerobic and anaerobic conditions and is thermotolerant, growing in temperatures up to 42°C.^{6,8}

In both immunocompromised and immunocompetent patients, *M. indicus* is a rarely described cause of fungal necrotizing fasciitis. Table 1 summarizes the above case and 9 other cases so far described, diagnosed by culture or nucleic acid testing, or both.^{11–19} Half of the cases described originated in the GI or hepatobiliary tracts, with the heart, skin, genitourinary tract, and bone reported as other sites of infection. Infection developed in patients with and without foreign bodies, and in those with and without immunocompromising conditions, exemplifying the diversity of pathogenesis. Only four patients had a described underlying malignancy and resulting immunodeficiency. Three of 10 described patients died, while four were left with severe morbidities, such as limb amputation and hemicolectomy. Six of the 10 received surgical intervention. In these case reports, many patients had radiographic findings of abscesses and most required prolonged courses of antifungals, if not also surgical debridement and even amputation of the affected limb. The rarity of the organism in infections and lack of interpretative criteria from antifungal susceptibility testing results cause treatment dilemmas in drug choice and duration, given the paucity of in vitro efficacy of antifungals. Given the high morbidity and mortality, a combination of surgical intervention with prolonged antifungal therapy is often warranted for *Mucorales* infections, especially in immunocompromised hosts.

Our patient had been on VRC for fungal infection prophylaxis at the time of her infection. As VRC is not active against *Mucorales*,²⁰ this raises concern about breakthrough *Mucor* infections during VRC prophylaxis. Koteda, et al describe a fatal case of breakthrough *M. indicus* in a 62-year-old female with ALL also on VRC prophylaxis, who developed GI infection.¹⁴ In comparing risk factors for 27 adult patients with mucormycosis (six of whom had mixed mold infections), matched by underlying leukemia or bone marrow transplant, Kontoyiannis, et al found VRC prophylaxis to be an independent risk factor for developing mucormycosis with an increased odds ratio (OR) of 10.37 (95% CI, 2.76–38.97). Patients with mucormycosis were also significantly more likely to have received VRC prophylaxis than those with invasive aspergillosis (OR 20.30; 95% CI, 3.85–108.15).²¹ The authors do not conclude that VRC prophylaxis is necessarily a cause of breakthrough *Mucorales* infections, citing the need for larger, prospective studies, but speculate that non-*Aspergillus*, VRC-resistant organisms may be selected for by the use of VRC prophylaxis.

In a large retrospective study, Prasad et al examined the incidence of and risk factors for developing mucormycosis, and included the use of VRC prophylaxis.²² They used the Pediatric Health Information System database and included all patients 18 years old or younger given a discharge diagnosis of mucormycosis according to the ICD, 9th version, clinical modification code. One hundred fifty-six unique pediatric patients with a mean age of 9.6 years were identified over a 7-year period. More than half of these children had a malignancy (58%) and 32% had a hematologic/immunologic condition. Thirty-nine patients (25%) died during their hospitalization. However, their data show that despite an overall increase in use of VRC prophylaxis in all hospitalized patients and concern for rapidly rising rates of mucormycosis in adult patient populations, there was no significant increase in mucormycosis over the study period. VRC is increasingly being used for prophylaxis, empirical, preemptive, and targeted treatment of invasive aspergillosis. The observations and concerns about an increase in incidence of *Mucorales* infections could simply be a result of changing immunosuppressive regimens that confer a greater risk for infection by rare molds. POS has been proposed and is being used in some centers for broad-spectrum antifungal prophylaxis.²³ Its reported coverage of both *Mucorales* and *Aspergillus* organisms may make it ideal.²⁴ However, it is currently not FDA approved for children under 13 years of age, and because of variable bioavailability, drug monitoring through serum levels is not always reliable. Kishel and Spivik also report a breakthrough case of *Mucorales* and *Aspergillus* invasive fungal sinusitis in a 49-year-old patient with leukemia who had been on POS, though mention the patient may not have received instruction on the specifics of how to take the medicine and no blood levels are mentioned in the paper.²⁵

4 | SUMMARY

We present a case of a 4-year-old female with non-fatal *M. indicus* cellulitis, myositis, and necrotizing fasciitis successfully treated with 10 months of antifungal therapy after multiple surgical debridements. The source of infection was never discovered. With newer technology becoming more widely available to identify *Mucorales* down to the species level, it is expected that the true incidence of *M. indicus* will become more apparent, as only 9 other cases have been reported in the literature to date. The need for further understanding of risk

factors, such as antifungal prophylaxis exposure, and organism susceptibility testing to help guide treatment is crucial.

Abbreviations:

5-FC	flucytosine
°C	degrees Celsius
ALL	acute lymphoblastic leukemia
AmB	amphotericin B
BID	bis in die (twice daily)
CI	confidence interval
cm	centimeter
CT	computed tomography
CV	cardiovascular
DCMP	dilated cardiomyopathy
Et al	et alia (and others)
F	female
FDA	Food and Drug Administration
FLU	fluconazole
FNA	fine needle aspiration
g	gram
GCSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GVHD	graft-vs-host disease
I&D	incision and drainage
ICD	International classification of disease
ITR	itraconazole
IV	intravenous
Kg	kilogram
L-AmB	liposomal amphotericin B
LVAD	left ventricular assist device

M	male
M.	Mucor
MDS	myelodysplastic syndrome
Mg	milligram
ml	milliliter
Mos	months
MRI	magnetic resonance imaging
MVA	motor vehicle accident
NA	not applicable
OR	odds ratio
PO	Per os (by mouth)
POS	posaconazole
RLQ	right lower quadrant (of abdomen)
RUQ	right upper quadrant (of abdomen)
s/p	status post
VRC	voriconazole

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FIGURE 1.

A, Magnetic resonance imaging of the patient's pelvis revealed cellulitis and fasciitis with bilateral inguinal small abscesses extending across the lower abdominal wall, no free air but bilateral adjacent myositis of the iliopsoas, pectineus, abductor brevis, and longus muscles. Largest abscess measured at 1.53×0.68 cm B, 200 $\times$ (power of microscope) Gomori Methenamine Silver Stain of groin tissue from first exploratory surgery. Fungal elements are black and are seen surrounding and invading a blood vessel. C, Pauciseptated hyphae, sporangiophores, and sporangia (100 $\times$ Lactophenol cotton blue stain). D, Sporangiospores inside sporangium along with free sporangiospores (1000 $\times$ Lactophenol cotton blue stain)

A review of all cases of necrotizing fasciitis caused by *Mucor indicus* reported in the literature (by age of patient)

TABLE 1

Reference (year)	Our case	de Repentigny (2008) ¹²	ter Borg (1990) ¹⁹	Oliver (1996) ¹⁷	Aboltins (2006) ¹¹	Deja (1998) ¹³	Sobel (2001) ¹⁸	Luo (2014) ¹⁵	Koteda (2013) ¹⁴	Mata-Essayag (2001) ¹⁶
Case	1	2	3	4	5	6	7	8	9	10
Age (years)/sex	4/F	6 mo/F	27/F	39/M	43/M	48/M	56/F	58/M	62/F	82/F
Predisposing conditions	Pre-B-cell ALL	DCMP s/p LVAD	T-cell ALL	MDS, GVHD	None	MVA, Craniectomy	None	Tibial injury, debridement, and skin graft	ALL	None
Presenting signs/symptoms	Acute groin pain with necrotizing fasciitis	CV collapse, massive bleeding	Fever, abdominal pain, diarrhea	Abdominal pain	Acute abdominal pain, diarrhea, and fever	GI bleeding	Vulvovaginal discomfort, vaginal discharge	Tibial ulcer	Fever	Fever, necrotizing fasciitis of left knee
MRI/CT	Cellulitis, inguinal abscess, myositis	NA	Liver abscesses	Liver abscesses with spread to diaphragm and abdominal wall	Thickening of the wall of the cecum, stranding of the surrounding fat	NA	NA	NA	Sigmoid colon perforation and liver space occupying lesion	NA
Site(s) of <i>M. indicus</i> isolated	Groin abscesses and lymph nodes	Ascending aorta	Ileocecal region, liver	Liver abscess	Abdomen, blood	Stomach, intestines	Vagina	Pretibial area	Colon, liver	Left knee necrotic tissue
Treatment and duration (when cited)	L-AmB (2 mo) plus surgical resection plus POS (8 mo)	–	AmB and 5-FC (duration unknown) plus FNA	AmB (5 mo) plus surgical resection plus 5-FC (5 mo)	AmB (6 wk)	AmB (33 d) plus Colectomy	3% AmB cream (3 wks)	AmB (47 d) plus Debridement then ITR (3 mo)	VRC (40 d) plus I&D then AmB (1 d)	AmB plus Amputation then FLU (3 mo)
Outcome	Recovery by 10 mo	Deceased	Deceased	Recovery by 23 mo	Recovery by 3 wk	Recovery by 6 mo	Relapsed once, recovery by 12 mo	Recovery by 3 mo	Deceased	Recovery by 12 mo