Published in final edited form as:

Pediatr Infect Dis J. 2016 April ; 35(4): 455–457. doi:10.1097/INF.0000000000001038.

SUBCUTANEOUS *COLLETOTRICHUM TRUNCATUM* INFECTION IN A CHILD

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Abstract

Human infection with *Colletotrichum* species is typically limited to ophthalmologic manifestations. We present the first reported pediatric case of subcutaneous *Colletotrichum truncatum* infection. This case highlights the potential importance of *C. truncatum* as an agent of subcutaneous or disseminated disease in immunocompromised children.

Keywords

fungal infection; immunocompromised host

A 4-year-old boy receiving chemotherapy for stage III, high-risk neuroblastoma developed 2 skin lesions. The lesions developed while the patient was receiving cefepime during a period of profound neutropenia 11 days after the completion of cycle 5 of induction chemotherapy with cisplatin and etoposide per Children's Oncology Group study ANBL0532. Singular, round, nontender, black necrotic-appearing plaques consistent with ecthyma gangrenosum evolved from erythematous plaques. They were present on the right side of the face and the dorsal aspect of the right foot and measured 1.5 cm and 1 cm in diameter, respectively. There were no known relevant dietary or environmental exposures. The patient had been receiving a neutropenic diet in the hospital in the weeks preceding the presentation. There was no known history of injury or contaminated trauma to the affected areas, although the facial lesion developed underlying tape used to hold a nasogastric tube in place. Vancomycin and voriconazole were added empirically to his prior antimicrobial regimen consisting of cefepime, and dermatology consultation was requested to obtain a diagnostic biopsy.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

The authors have no other funding or conflicts of interest to disclose.

A punch biopsy of the right foot lesion was performed. Gomori methenamine silver stain revealed numerous fungal hyphae infiltrating throughout the dermis and subcutaneous fat with minimal associated inflammation. Fungal elements and fibrin thrombi occluded many of the dermal vessels, and organisms were present around nerve twigs. The hyphae demonstrated variable morphology with some elements demonstrating septation and irregular branching and occasional broad hyphal elements with irregular shapes (Fig., Supplemental Digital Content 1, <http://links.lww.com/INF/C373>). Liposomal amphotericin B (L-amp-B) was added to the antimicrobial regimen. Otolaryngology and orthopedic surgery services were consulted for surgical debridement. Two days after diagnostic biopsy, the patient underwent operative excision of the right facial and lower extremity lesions, as well as nasal endoscopy. Surgical pathology findings were consistent with the diagnosis of angioinvasive fungal infection; however, the surgical margins were free of fungal hyphae.

Repeated bacterial and fungal cultures obtained from blood were negative. Blood 1,3 beta-D-glucan testing and aspergillus antigen testing were also negative. Computed tomographic scans of the sinuses, chest, abdomen and pelvis, as well as brain magnetic resonance imaging, were obtained both at the time of development of the skin lesions and after neutrophil count recovery and demonstrated no evidence of solid organ infection or dissemination to other sites. Nasal endoscopy and ophthalmologic evaluations were also unremarkable.

Before fungal identification was available, antifungal susceptibility testing was performed demonstrating minimal inhibitory concentrations of 0.125, 0.25, 0.25 and 0.25 µg/mL to amphotericin B, micafungin, posaconazole and voriconazole, respectively, and a minimal lethal concentration of 0.5 to amphotericin B. The fungal organism isolated from skin biopsy culture produced dark, irregularly shaped appressoria on potato flakes agar and hyaline, single-celled falcate conidia within setal acervuli on carnation leaf agar after 6 days incubation at 25°C. Although the morphologic features of *Colletotrichum dematium* and *Colletotrichum truncatum* are indistinguishable, DNA sequencing of the internal transcribed spacer, β-tubulin and glycerol-3-phosphate dehydrogenase targets was used to identify the species as *C. truncatum* (University of Texas Health Science Center Fungal Testing Laboratory, San Antonio, TX).^{1,2} After 3 weeks of combination antifungal therapy with L-amp-B and voriconazole, L-amp-B was discontinued. Voriconazole was continued, and 4 months later, the patient underwent autologous stem cell transplant after a high-dose chemotherapy regimen consisting of melphalan, carboplatin and etoposide. In addition to voriconazole, he received daily micafungin through neutrophil nadir and recovery. No *Colletotrichum* disease recurrence or other fungal infectious complication occurred in the post-transplant period. After approximately 7 months of antifungal therapy, voriconazole was discontinued due to a severe photosensitivity reaction. At most recent follow-up, 20 months after the initial presentation and surgical resection of the lesions, the patient had no evidence of *Colletotrichum* recurrence or other fungal infection since the discontinuation of antifungal therapy.

DISCUSSION

Organisms in the genus *Colletotrichum* are important plant pathogens, primarily in tropical and subtropical regions, and are primarily described as causing anthracnose diseases among many fruits, coffee berries and other crops, including maize, sugar cane and sorghum. The taxonomy and nomenclature of this group of organisms are a subject of some uncertainty. Identification has been complicated by difficulties in distinguishing *Colletotrichum* spp. morphologically; however, recently >60 species have been described based on morphologic characteristics, host specificity, DNA analysis and phylogenetic systematics.³ Although increasingly reported in recent years, human infection with *Colletotrichum* spp. is rare. At least 6 *Colletotrichum* spp. have been associated with human disease, including *C. dematium*, *Colletotrichum coccodes* (reported as *Colletotrichum atramentarium*), *Colletotrichum gloeosporioides*, *Colletotrichum graminicola*, *Colletotrichum crassipes* and *Colletotrichum capsici* (now considered by many researchers as synonymous with *C. truncatum*).^{1,3,4} Ocular disease, primarily keratitis or endophthalmitis, is the most common manifestation of *Colletotrichum* infection, with disease often occurring as a result of traumatic or iatrogenic inoculation of vegetative material.

Subcutaneous infections caused by *Colletotrichum* spp. have also been reported, primarily in immunocompromised hosts. The first cases of subcutaneous infections associated with *Colletotrichum* spp., specifically *C. coccodes* and *C. gloeosporioides*, in the United States were reported from our institution in 2001.⁵ In each case, adults with iatrogenic immunosuppression for hematologic malignancies presented with single erythematous nodular lesions approximately 2 weeks after immune suppression was initiated. Two of these patients improved with systemic antifungal therapy, whereas the third patient eventually succumbed due to progressive pneumonia. Autopsy specimens from a cavitary lung lesion demonstrated septate, acute-angled branching hyphae infiltrating into vascular spaces, but cultures for fungi were negative. One additional report of a subcutaneous cyst caused by *C. crassipes* exists in an adult male status post-renal transplant in Brazil that was treated with surgical excision and did not recur or disseminate.⁶ To our knowledge, no other cases of subcutaneous or disseminated *Colletotrichum* infection exist, and ours is the first case of deep mycosis caused by *Colletotrichum* species reported in a child. Although the presence of skin lesions at 2 remote sites in our patient may suggest dissemination of fungal disease, repeated blood cultures were negative as were evaluations for central nervous system and solid organ fungal infection. Alternatively, these distinct remote lesions could have resulted from either autologous or iatrogenic cutaneous inoculation from one site to the other after minor skin trauma.

C. truncatum was only recently recognized as a human pathogen. To date, all prior reports of human cases of *C. truncatum* infection were limited to ocular manifestations (Table 1). In 2011, 5 cases of ocular infection by *C. truncatum* were reported from India.¹ Each of these isolates was initially presumptively identified as *C. dematium* based on morphologic characteristics, thus underscoring the difficulties in morphologic identification of *Colletotrichum* organisms at the species level and the important role of a polyphasic molecular approach in the speciation of this genus.² An additional episode of keratitis associated with *C. truncatum* based on molecular diagnostic techniques has been reported

from Canada, while one episode from Nepal was identified as *C. capsici* by morphologic characteristics.^{4,7,8} To the authors' knowledge, this is the first case in which *C. truncatum* has been reported to cause subcutaneous manifestations.

Treatment of subcutaneous angioinvasive fungal infections should involve surgical excision of localized infection when feasible. The presence of multiple lesions or disseminated disease requires systemic antifungal therapy. No consensus exists regarding the optimal first-line antifungal agent to treat *Colletotrichum* infections. Data are scarce regarding the clinical responses and susceptibilities to systemic antifungal therapeutic agents for *Colletotrichum* spp. in subcutaneous disease. In a review of isolates from the Fungus Testing Laboratory at the University of Texas Health Sciences, all *Colletotrichum* isolates tested (8/8) demonstrated in vitro susceptibility to amphotericin B.⁹ Other studies evaluating *Colletotrichum* isolates from subjects with ocular or cutaneous disease have demonstrated nearly uniform susceptibility to amphotericin B (minimal inhibitory concentration <1 µg/mL) as well.¹⁰ While data are more limited for other systemic antifungal agents, *Colletotrichum* spp. have also demonstrated in vitro susceptibility to voriconazole although treatment failure has been reported with the use of topical (ocular) voriconazole in a case of *Colletotrichum* keratitis.¹¹ Variable in vitro susceptibility to miconazole, ketoconazole and itraconazole has also been demonstrated.^{1,9}

Acknowledgments

L.M.H. was supported by Fogarty International Center Grant Number R25TW009337 from the National Institutes of Health through Vanderbilt University.

The authors are grateful to the Fungal Testing Laboratory, University of Texas Health Science Center at San Antonio (Laboratory Director, Nathan P. Wiederhold, PharmD; Administrative Director, Deanna A. Sutton, PhD, MT) for their diagnostic expertise and input. They also thank Tanya Snyder, MT (ASCP), of the Clinical Microbiology Laboratory at Vanderbilt University Medical Center, for her expert technical assistance.

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TABLE 1

Reported Human Cases of *C. truncatum* Infection

Age/Sex	Country	Mode of Infection	Presumptive Morphological Identification	Identification by Internal Transcribed Spacer Sequencing	Treatment	Outcome	Reference
60/F	India	Trauma with wooden stick	<i>C. dematium</i>	<i>C. truncatum</i>	Therapeutic keratoplasty, oral and topical fluconazole	Atrophic bulbitis with staphylocoma	1
38/M	India	Subconjunctival injection of dexamethasone	<i>C. dematium</i>	<i>C. truncatum</i>	AmB, itraconazole, dexamethasone, pars plana vitrectomy	Clinical improvement	1
70/M	India	No trauma	<i>C. dematium</i>	<i>C. truncatum</i>	Therapeutic keratoplasty	Clinical improvement	1
58/M	India	Insect fall	<i>C. dematium</i>	<i>C. truncatum</i>	Therapeutic keratoplasty	Corneal opacity	1
50/M	India	Trauma with wooden stick	<i>C. dematium</i>	<i>C. truncatum</i>	AmB, pars plana vitrectomy	Partial improvement	1
87/M	Canada (Jamaica)		NA	<i>C. truncatum</i>	AmB, evisceration and reconstruction	No recurrence after evisceration	8
Unknown	Nepal	Unknown	<i>C. capsici</i> *	NA	Unknown	Unknown	6

* *C. capsici* now considered by many researchers synonymous with *C. truncatum*, part of *C. truncatum* spp. complex (Damm and Hyde).

AmB indicates amphotericin B.