CASE REPORT

Surgical management of subcutaneous *Colletotrichum gloeosporioides*

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SUMMARY

A 52-year-old male patient with a history of sarcoidosis and over 10 years of chronic low-dose glucocorticoid use, cirrhosis and type 2 diabetes mellitus presented with two painful, enlarging subcutaneous nodules ultimately identified as *Colletotrichum gloeosporioides*. Two attempts at needle aspiration of the larger nodule resulted in rapid reaccumulation. Complete surgical excision of both nodules resulted in complete resolution without the use of any concomitant antifungals. Patient had no recurrence at 2 years of follow-up.

BACKGROUND

Colletotrichum gloeosporioides is a relatively uncommon cause of subcutaneous nodules. Our case demonstrates that serial needle aspiration is unsuccessful, while complete excision was curative. Although antifungals were a consideration, we elected to withhold these given the setting of this patient's cirrhosis and elevated transaminases. Our case demonstrates that concomitant antifungals may not be required even after initial, unsuccessful needle aspirations.

CASE PRESENTATION

A 52-year-old African-American male patient with a history of sarcoidosis and over 10 years of chronic low-dose glucocorticoid use, cirrhosis and type 2 diabetes mellitus presented to the dermatology clinic with an extra-articular subcutaneous nodule on his left elbow for several years. Few months prior to presentation the lesion had become more painful and increased in size. He denied fever, chills, night sweats and weight loss, and he recalled no recent trauma to the area. On initial examination, the mass was 3 cm, soft, mobile and tender without increased warmth. Plain film revealed a soft tissue mass without evidence of arthritis, fracture or bone destruction. He had exertional dyspnoea, stable for the past 3 years. Medical history was significant for sarcoidosis with pulmonary, liver and cutaneous involvement. He was maintained on oral prednisone of 10 mg daily for sarcoidosis while awaiting liver transplant due to cirrhosis.

He was subsequently referred to an orthopaedic surgeon who performed aspiration of the lesion and 3.5 mL of blood-tinged purulent material was recovered. Near the end of the procedure and with the needle withdrawn, an 8 mm foreign body with the appearance of a thorn was also removed. The lesion reaccumulated within days, and repeat aspiration was performed 2 weeks later and 1.5 mL of

similar fluid was obtained. Patient received 1 week courses of amoxicillin following the aspiration on both occasions. The culture from initial aspiration was reported as *Candida lipolytica* and the second aspirate culture was identified as *Dactylaria constricta*. This latter culture was sent to the Fungus Testing Laboratory at the University of Texas Health Science Center at San Antonio for further identification. As the area fluid had reaccumulated for a third time, consultation was directed to infectious diseases for further recommendations.

On examination, the patient was afebrile. Skin examination revealed multiple discrete lesions from cutaneous sarcoidosis (figure 1). He had hepatomegaly, clubbing of upper extremities and pitting oedema of the lower extremities. The left elbow revealed a mobile, mildly tender, rubbery mass measuring 1.5×2 cm (figure 2). A similar but smaller lesion of 0.5 cm was also noted on the flexor aspect of the left wrist.

Laboratory data revealed a leucocyte count of 5300 cells/mL, haemoglobin of 11.9 g/dL, platelet count of 200 000/mL, aspartate aminotransferase of 162 U/L, alanine aminotransferase of 111 IU/L, alkaline phosphatase of 684 U/L, albumin of 2.6 g/dL, protein of 7.9 g/dL, bilirubin of 4.3 mg/dL and creatinine of 0.97 mg/dL. Given his underlying liver disease, we recommended complete excision at both sites without any antifungal agents. The histopathology of the excised lesions revealed the presence of fungal hyphae consistent with *C. gloeosporioides*, as well as acute and chronic inflammation, inflamed granulation tissue, and foreign body giant cell granuloma (figure 3). The

Figure 1 Close up of patient's cutaneous sarcoidosis lesion.

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Figure 2 Left elbow revealed a mobile, mildly tender, rubbery mass measuring 1.5x2 cm.

culture from the excised nodules was identified as *C. gloeosporioides* (figures 4 and 5). Cultures of the prior two aspirates were also identified as *C. gloeosporioides* by the reference mycology laboratory. Antifungal susceptibilities were obtained for amphotericin (MIC 1), itraconazole (MIC 2) and voriconazole (MIC 2).

INVESTIGATIONS

Culture of excised nodules, histopathology of excised nodules, cultures of prior aspirates.

TREATMENT

Surgical excision without antifungals.

OUTCOME AND FOLLOW-UP

Two days after the surgical excision of the lesions, the patient developed localised fluctuant swelling at the postoperative site. Repeat aspiration of the fluid collection was consistent with

Figure 3 Histopathology section of the lesion.

Figure 4 Gross appearance of culture from excised nodule demonstrating brown-black pigmentation.

postoperative seroma and cultures from this fluid were negative for fungus. Patient received no antifungal agents and at 2 years of follow-up, the patient continued to do well with no further recurrence of the nodules.

DISCUSSION

PubMed search of the English literature was performed using key words: *Colletotrichum*, *Colletotrichum gloeosporioides* and *gloeosporioides* treatment. To our knowledge, this is the third case of infection due to *C. gloeosporioides* presenting with a subcutaneous nodule.

In 1974, Ajello *et al*¹ introduced the collective term phaeohyphomycosis (PHM) to describe a collection of mycoses caused by diverse genera and species of dematiaceous fungi. It is caused by fungi that exhibit septate, dark-walled mycelial elements in the host's tissues as a histological characteristic. Mycotic cysts are a localised form of PHM, which are asymptomatic subcutaneous lesions that can develop from traumatic implantation of the fungi into the tissues. While etiological agents include *C.*, *Bipolaris*, *Exophiala*, *Phoma*, *Curvularia*, *Phialophora*, *Alternaria* and *Exserohilum*, the most frequent causes are *E. jeanselmei*, *P. verrucosa* and *Wangiella dermatitidis*.² These fungi are found widespread in moist environments, such as decaying vegetation, wood and soil. Factors that predispose to PHM include organ transplantation, prolonged hospitalisation, malignancy, endocrinopathies and corticosteroid therapy;³ however, infections can occur in immunocompetent hosts. The

Figure 5 Conidia of *Colletotrichum gloeosporioides*, lactophenol cotton blue.

most common sites of non-cutaneous infections are the sinuses, lungs and brain.⁴

Colletotrichum spp are typically plant pathogens with worldwide distribution, though they are found mainly in subtropical and tropical regions. Key morphological features include acervular conidiomata, often with setae (dark-pigmented, unbranched, thick-walled sterile hyphae), producing elongated conidia. They can develop appressoria (flat swellings at the end of hyphae) to attach to host surfaces before penetration of tissue.⁵ There are five major species of *Colletotrichum* that can cause human infections: *C. dematium*, *C. coccodes*, *C. gloeosporioides*, *C. graminicola* and *C. crassipes*. The most common form of infection is keratitis.^{6–8}

Subcutaneous mycotic cysts are often preceded by a history of trauma from a wooden splinter or thorn. Lesions begin as small papules that evolve into larger subcutaneous purulent cysts. Early lesions may be similar to other cutaneous diseases, such as cutaneous leishmaniasis, lobomycosis, paracoccidioidomycosis, coccidioidomycosis and sporotrichosis. The differential diagnosis of subcutaneous PHM includes lipomas, epidermal cysts and foreign body granuloma.⁴ Skin biopsy may show neutrophil-rich abscesses and granulomatous inflammation with histiocytes, lymphocytes and multinucleated giant cells.⁹ As in our case, a thorn or wooden splinter along with a foreign body granulomatous reaction can be observed.

In researching the literature for subcutaneous PHM from *Colletotrichum* spp (table 1), we found one case of *C. crassipes* in a renal transplant patient,¹⁰ two cases of *C. coccodes* in patients with non-Hodgkin's lymphoma (NHL),¹¹ and two cases of *C. gloeosporioides* in a patient with acute lymphocytic leukaemia¹¹ and in a patient with diabetes on oral corticosteroids,¹² similar to our patient. An additional case of *Colletotrichum* was described in a patient with NHL, but the isolate was not identified to species level.¹³ All cases, except for one where a site was not described, involved a subcutaneous site of an extremity. Two cases in patients with NHL on chemotherapy suggested the possibility of disseminated disease with pulmonary cavitation.^{11–13} Each of these patients died and autopsy was limited to the lungs, with pathology revealing septate, acute-angled branching hyphae focally infiltrating into vascular spaces. In neither case was the author able to confirm a pathogen in the lungs by fungal culture.

Treatment of subcutaneous PHM is based on limited information from case reports or small case series. The accepted treatment of choice is surgical excision, and antifungal therapy is recommended for recurrence and in immunocompromised patients. Case reports have documented efficacy of flucytosine 150 mg/kg/day, itraconazole 200 mg/day, ketoconazole 200 mg/day, and intravenous or intralesional amphotericin B.⁴ Experience is greatest with itraconazole and in doses up to 600 mg/day, it may be the most effective agent for subcutaneous PHM, including in those with disease refractory to other antifungals.¹⁴ While itraconazole and voriconazole demonstrate the most consistent in vitro activity,¹⁵ ketoconazole is active in vitro but is poorly tolerated. Fluconazole has negligible activity against dematiaceous fungi and essentially no role in therapy given the available alternatives.¹⁶

Antifungal susceptibility testing specifically for *Colletotrichum* spp has been examined in few reviews. In 16 *Colletotrichum* isolates from very diverse sources, MICs in general were low for amphotericin B (with only 1 isolate higher than 1 µg/mL), miconazole, itraconazole and ketoconazole.¹² In vitro antifungal susceptibility data generated at the Fungus Testing Laboratory¹⁷ using MICs to approximate resistance

suggested 8 of 8 *Colletotrichum* isolates susceptible to amphotericin B, 4 of 7 isolates susceptible to itraconazole, 2 of 2 isolates susceptible to miconazole, 1 of 1 isolate susceptible to ketoconazole and 1 of 6 isolates susceptible to fluconazole. In the three case series, including one *C. gloeosporioides* and two *C. coccodes* isolates, the MIC ranged from 0.06 to 0.5 µg/mL for amphotericin B and 0.25 to 2 µg/mL for itraconazole,¹¹ while our *C. gloeosporioides* isolate had an MIC of 1 µg/mL for amphotericin B and 2 µg/mL for itraconazole.

In our review (table 1) of subcutaneous PHM cases from *Colletotrichum*, the five cases reported in the USA occurred in southeastern states, consistent with the known subtropical distribution of *Colletotrichum*. Antifungals were given in 4 of 7 cases; amphotericin B and itraconazole were given either sequentially or in at least one case, simultaneously. Combination therapy may be considered in refractory or severe cases of PHM, but has not been evaluated specifically in *Colletotrichum*. Synergy has been demonstrated in vitro when either amphotericin B or itraconazole is combined with flucytosine, but synergy between itraconazole and amphotericin has not been consistent.⁴ In a bone marrow transplant patient who had undergone several wide margin resections for *E. jeanselmei* subcutaneous PHM, the addition of itraconazole 600 mg/day to a 3-week course of combined amphotericin B and flucytosine resulted in cure at 15 months of follow-up.¹⁸ In a review of 101 primary central nervous system PHM infections, the combination of amphotericin B, flucytosine and itraconazole was associated with improved survival.¹⁹

No standard of treatment exists for subcutaneous PHM. Correlation between MIC data and clinical outcome data is sparse and complicated by lack of long-term follow-up reported in the literature. As we were trying to avoid potentially hepatotoxic medications in our patient with cirrhosis, surgical excision alone was curative at 2 years of follow-up. Although two other cases of *C. gloeosporioides* PHM have been reported, one case involved treatment with antifungals without further follow-up described beyond hospital discharge while in the other case, the patient died in a motor vehicle accident prior to the starting of the treatment. Our case of *C. gloeosporioides* PHM represents the longest follow-up to date. However, caution to our approach is warranted in that our patient did not have the degree of immunosuppression as did the other patients in our review.

CONCLUSION

C. gloeosporioides is a plant pathogen that can cause opportunistic infections in immunocompromised patients. Even though the incidence is extremely rare, infections can potentially be fatal if dissemination occurs. Despite our patient not remembering sustaining an injury with a cactus, it is likely that the thorn found in the nodule was responsible for introducing the infection in the patient's elbow. The patient was active in the military in the decades of the 1970s and 1980s, and he was exposed to different environments during his training and duties. Since he is immunocompromised due to his steroid use, diabetes and cirrhosis, we felt that eradication of the infection was essential as he is currently on the liver transplant list with expectation of even greater immunosuppressive therapy post-transplant. Our patient is doing well with surgery alone and we feel this is an effective way of treating localised infection with *C. gloeosporioides*. As our experience of treating *C. gloeosporioides* is limited, we recommend that patients be treated on an individualised basis until more cases and outcomes are reported.

Table 1 Review of patients with subcutaneous phaeohyphomycosis due to *Colletotrichum* species

Reference	Age/ sex	Comorbid condition	Immunosuppression	Patient residence	Clinical presentation	Site	Preceding event	<i>Colletotrichum</i> species	Invasive fungal disease	Therapy	Outcome
¹⁰	34/M	Renal transplant	Cyclosporine prednisone azathioprine	Sao Paulo, Brazil	2.5 cm non-tender, non-erythematous nodule	Right leg	Gardener, but no reported trauma	<i>C. crassipes</i>	Absent	Surgical excision	No recurrence at 1 year
¹¹	34/M	Acute lymphocytic leukaemia, relapse	Vincristine daunorubicin prednisone l-asparaginase	Tennessee, USA	1.2×1.2 cm tender, erythematous nodule, low-grade fever	Right forearm	Fell on cactus 4 months prior; chemotherapy-induced neutropaenia	<i>C. gloeosporioides</i>	Absent	Amphotericin B 0.5 mg/kg/ day×3 days, then oral itraconazole 200 mg twice daily×3 weeks	Improved at discharge
¹¹	47/M	Non-Hodgkin's lymphoma; stem cell transplant	Cyclophosphamide bleomycin carmustine etoposide	Mississippi, USA	1.0×1.5 cm tender, erythematous nodule with central pustule	Left forearm	Antecedent trauma history absent; chemotherapy-induced pancytopenia	<i>C. coccodes</i>	Absent	Amphotericin B 0.5 mg/kg/ day×6 days, then itraconazole 200 mg twice daily×14 days	Nodule resolved at discharge
¹¹	58/M	Non-Hodgkin's lymphoma; bone marrow transplant	Cyclophosphamide bleomycin carmustine etoposide	Alabama, USA	0.5×0.5 cm tender, erythematous papule with central pustule; fever; RLL focal consolidation with cavitation of 3.8 cm	Left forearm	No reported trauma; chemotherapy-induced pancytopenia	<i>C. coccodes</i>	Autopsy sections of RLL cavity with septated acute-angled branching hyphae infiltrating into vascular spaces. No conidia. Cultures negative	Amphotericin B 1 mg/kg/day and concomitant oral itraconazole 200 mg thrice daily	Progressive respiratory failure and hypotension. Died on hospital day 34
¹²	56/M	Diabetes	Prednisone 20 mg/day	Parana, Brazil	Multiple 1–3 cm nodular, erythematous, violaceous, solitary or confluent lesions; additional macular lesions	Left forearm, elbow	Traumatic injury to left hand by rotten wood 1 year prior	<i>C. gloeosporioides</i>	Absent	Patient died in motor vehicle accident prior to establishing treatment	Unknown
¹³	58/M	Non-Hodgkin's lymphoma; bone marrow transplant	Intrathecal cytarabine, methotrexate; cyclophosphamide doxorubicin vincristine prednisone	Tennessee, USA	Cutaneous macular, lesion; fever, dyspnoea, RLL lung cavity of 3 cm	Not described	Not reported	Not identified to species level	Autopsy limited to lungs with septate, acute-angled branching hyphae, focally infiltrating into vascular spaces. No conidial heads seen. Fungal cultures negative	Amphotericin B and oral itraconazole	Died from invasive pulmonary fungal disease
Our case	52/M	Cirrhosis, diabetes, sarcoidosis	Prednisone 10 mg/day	Texas, USA	3 cm and 0.5 cm tender, non-erythematous, nodules	Left elbow, left wrist	Presumed remote history of cactus thorn injury	<i>C. gloeosporioides</i>	Absent	Surgical excision	No recurrence at 2 years

RLL, right lower lobe.

Learning points

- ▶ *Colletotrichum gloeosporioides* is a plant pathogen than can cause opportunistic infections in immunocompromised hosts.
- ▶ Management of subcutaneous nodules with needle aspiration was unsuccessful.
- ▶ Surgical excision without concomitant antifungals resulted in cure for our patient at 2 years of follow-up.

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