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Successful management of *Lomentospora prolificans* septic arthritis and osteomyelitis in an immunocompetent child: A case report

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ABSTRACT

Available online We report a case of limb-threatening *Lomentospora prolificans* elbow infection in a 3-year-old immunocompetent boy following a closed fracture. Resolution of infection was achieved following combined aggressive debridement, combined antifungal therapy, voriconazole-loaded bone cement, and antiseptic joint irrigation. This highlights the need for early diagnosis and multi-modal surgical, medical and other novel adjunctive therapies in managing these difficult-to-treat infections. Increased research and improved access to novel antifungal drugs are essential to enhance treatment options for intrinsically multidrug-resistant fungal infections.

1. Introduction

Invasive infections due to *Lomentospora prolificans*, formerly *Scedosporium prolificans*, are increasingly reported in the hot, dry climates of Australia, Spain and the United States. [1]. *L. prolificans* is a filamentous fungus that is found in a range of environmental reservoirs including soil and plant matter. It is known to cause severe infections in both immunocompromised and immunocompetent hosts. In immunocompromised individuals, it may cause severe pulmonary or disseminated infections that are often fatal. Immunocompetent patients may develop localised infections following trauma, including bone and joint infections that may necessitate limb amputation.

Lomentospora prolificans is intrinsically resistant to most antifungal agents and was identified as a priority pathogen in the World Health Organization's inaugural Fungal Priority Pathogen List in 2022 due to its clinical impact and the limited availability of effective antifungal treatments. [2]. Voriconazole and terbinafine have demonstrated synergistic effects *in vitro,* and are usually recommended in combination as empiric therapy. [3]. However, other treatment options are severely limited due to *L. prolificans*' intrinsic resistance to most antifungal agents. Novel therapies such as olorofim show promising *in vitro* activity but remain largely inaccessible, particularly for children, due to the absence of paediatric safety and dosing data. Reported *L. prolificans* infections in children are rare, further limiting the accumulation of clinical experience and the sharing of management strategies.

We report a case of septic arthritis and osteomyelitis of the elbow in a 3-year-old immunocompetent boy that occurred following operative repair of a closed fracture.

2. Case

A previously healthy 3-year-old boy (weight 14 kg) suffered a closed supracondylar fracture of the right humerus after falling on his elbow at a playground (day 0). There was no history of penetrating injury. He underwent closed reduction and internal K-wire fixation on day +1 at a local hospital, with no immediate post-operative complications. He was discharged with routine orthopaedic follow-up planned and received appropriate intraoperative prophylactic antibiotics. The patient had no significant medical history, recent travel, or notable exposure to animals, plants, or water preceding the injury.

Approximately three weeks post-injury, the child and family reported elbow pain. On day +25, K-wires were removed, revealing

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redness and discharge at the wire sites. There was no fever or swelling of the elbow. X-rays showed no abnormalities. He was treated with oral cefalexin for a suspected localised pin site infection.

The next day (day +26), the child was admitted to a different hospital due to increasing purulent discharge from the pin sites. His C-reactive protein (CRP) was elevated (68 mg/L, reference range: < 3mg/L) though he was afebrile and systemically well on admission. He was treated with intravenous (IV) cefazolin (50 mg/kg every 8 hours) and vancomycin (15 mg/kg every 6 hours) for suspected bacterial osteomyelitis. Despite this, he later developed fever and elbow swelling, and his CRP rose to 125mg/L. Joint washouts of the right elbow on day +30, +34 and + 36 revealed elbow joint purulence. On day +37, cultures from intraoperative tissue specimens from day +30, +34 and + 36 revealed a filamentous fungus. Histopathological examination showed acute inflammation with numerous neutrophils and histiocytes, focal granulation tissue, and reactive spindled histiocytes, without granulomata. The patient was commenced on IV voriconazole (9 mg/kg twice daily for 24 hours, followed by 8 mg/kg twice daily).

On day +38, the child was transferred to a tertiary paediatric center for specialised paediatric infectious diseases and orthopaedic care. The fungal isolates were noted to resemble *L. prolificans*. Terbinafine (6 mg/kg twice daily) was added to his voriconazole therapy, and antibiotics were discontinued. On day +39, a fourth washout revealed significant joint destruction, including erosion of the anconeus and extensor carpi ulnaris muscles, lateral ulnar collateral ligament and extensive bone loss. Intramedullary pus was observed in the distal humerus. In addition to saline washout, both posterior and anterior capsules were thoroughly debrided, and a radial synovectomy was performed. *L. prolificans* was ultimately confirmed on culture on day +50 and exhibited high minimum inhibitory concentration (MIC) values for all antifungal agents, including olorofim (Table 1). An immunological evaluation of the patient showed normal neutrophil function, lymphocyte subsets, and immunoglobulin levels.

The clinical team sought to access olorofim but were unable to do so, due to a lack of safety and dosing data for children under 6 years. On day +43, the serum voriconazole concentration was 3.71 mg/L. Voriconazole therapeutic drug monitoring revealed a median serum level of 2.5 mg/L (range 0.55–4.31 mg/L) throughout the treatment (Fig. 1).

Over the next two months, the patient underwent four additional operative debridement procedures. Despite ongoing combination antifungal therapy, *L. prolificans* continued to be cultured from intraoperative tissue (day +44).

To avoid amputation, further salvage interventions were implemented. On day +45, intravenous micafungin was added for potential synergistic benefits. Voriconazole-loaded polymethylmethacrylate (PMMA) bone cement was used to fill intra-articular bone defects on day +47 (later removed on day +75). Voriconazole (200mg powder for injection) was mixed directly into the bone cement (at a final concentration of 50mg/g) and the paste directly applied to the joint cavity on day +75, +79, and +82. Additionally, a 0.1 % betaine and 0.1 % polyhexanide antiseptic solution (Prontosan®) was applied during wound and deep tissue washouts on day +47, +75, +79, and +82.

Table 1
Minimum inhibitory concentrations for selected antifungal agents.

Drug	Minimum inhibitory concentration (μg/mL)
Amphotericin B	> 8
Anidulafungin	> 8
Micafungin	> 8
Itraconazole	> 8
Flucytosine	> 64
Posaconazole	> 8
Voriconazole	> 8
Itraconazole	> 16
Fluconazole	> 256
Olorofim[a]	0.125

[a] Testing for the novel agent olorofim was also performed at the request of the clinical team.

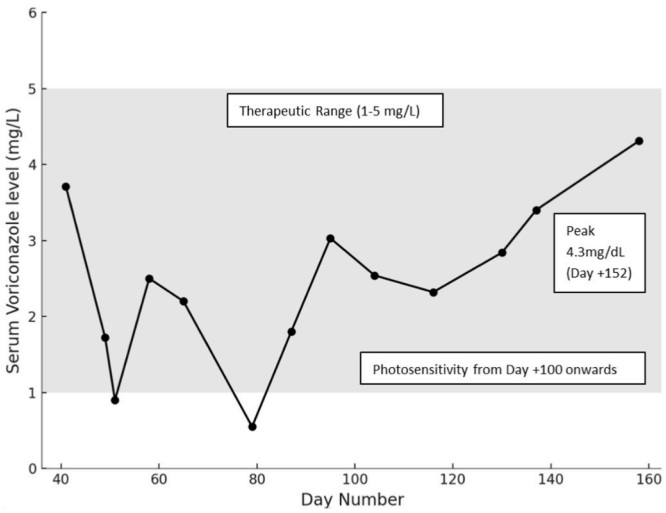

Fig. 1. Serum voriconazole concentrations over the course of treatment.

Imaging studies, including MRI (day +67) (Fig. 2A/B) and bone scintigraphy (day +68), revealed persistent septic arthritis and osteomyelitis. Due to refractory infection on day +70, alternative antifungal and adjunctive therapies were considered, such as miltefosine, granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon gamma, despite limited evidence for use of the latter in immunocompetent hosts.

Over time, the intraoperative appearance of the elbow improved, and subsequent operative samples yielded no growth of *L. prolificans*. Due to continued improvement, micafungin was discontinued on day +96. The patient was discharged home on day +102 on oral voriconazole and terbinafine dual antifungal therapy.

The patient faced complications from extended voriconazole therapy, including constipation, photosensitive dermatitis, alopecia, brittle nails, elevated liver enzymes, and sleep disturbance. Dermatological issues were addressed with sun avoidance, sunscreen, and emollients. The peak voriconazole level reached 4.3 mg/L on day +152. Voriconazole and terbinafine were discontinued on day +184 after a prolonged period of clinical stability and no signs of active infection. Subsequently, the patient's liver enzymes, hair, skin, and nails normalised. By day +352, improvements in physical activity and functional tasks were observed, although muscle atrophy, restricted elbow movement, and radiographic abnormalities (Fig. 2C/D) remained.

3. Discussion

This case highlights the challenges of managing *L. prolificans* infections, even in otherwise healthy children. The global incidence of *L. prolificans* infection is not well-defined, especially in children. Between 2000 and 2019, only 22 paediatric cases were reported worldwide, with 40 % (9/22) occurring in Australia. [4]. Similarly, among 233 adult cases reviewed from the same period, nearly half (109/233) were reported from Australia. [3]. A recent systematic review focused on 142 disseminated *L. prolificans* infections, mostly in immunocompromised patients [5]. Only five paediatric cases were identified, all involving multi-site disease. In contrast, localised osteoarticular infections have been described in immunocompetent children and are often associated with a history of penetrating injury (Table 2). Our patient had no identifiable penetrating injury or environmental exposure but developed a severe infection following orthopaedic surgery.

Combination antifungals have been a preferred strategy in the

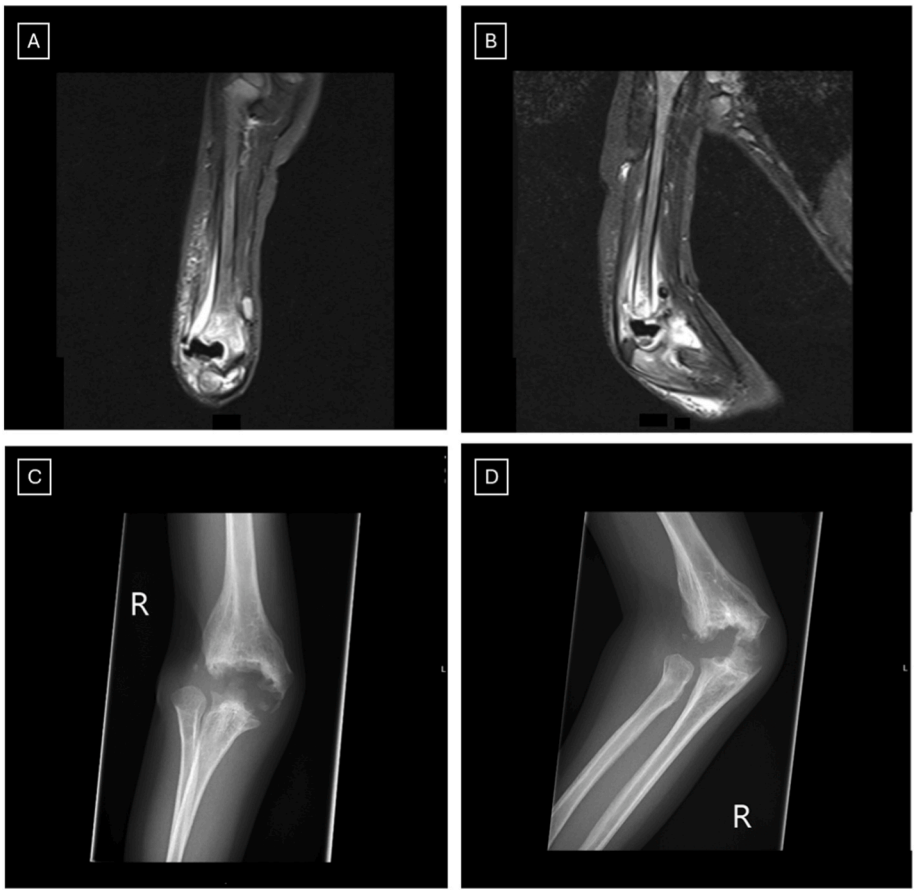

Fig. 2. Right elbow septic arthritis and osteomyelitis due to *Lomentospora prolificans* in a 3-year-old boy: Imaging findings
A: Magnetic resonance imaging (MRI) (sagittal) demonstrating moderate marrow oedema within the distal humeral metaphysis, with circumferential periosteal elevation and a hyperintense rind suggestive of periosteal reaction/granulation tissue. Cement seen within extensive osseous defects within the olecranon fossa.
B: MRI (coronal, post-contrast) demonstrating marked synovitis with joint capsule distension, particularly at the medial/ulnar aspect and radial head. In addition, there is diffuse soft tissue oedema and moderate reactive lymphadenopathy along the medial neurovascular bundle and in the axilla
C: X-ray (anteroposterior) demonstrating stable osseous defects in the capitellum and trochlea, with persistent smooth periosteal reaction.
D: X-ray (lateral) demonstrating unchanged osseous defect with persistent periosteal reaction.

management of *L. prolificans* infection owing to *in vitro* synergy and intrinsic resistance to conventional single antifungals. [3,13]. Voriconazole combined with terbinafine has been associated with the highest rates of treatment success compared with other regimens in adult patients and is a recommended first-line treatment regimen. [3, 13]. Alternative combination therapies, such as voriconazole with an echinocandin, have also shown *in-vitro* synergy [14] and some clinical success in case reports. [12]. Hence micafungin was added to the regimen for our patient. Adjunctive miltefosine is active i*n-vitro* and has also been reported as clinically efficacious as salvage therapy. [6,10].

Olorofim, a novel orotomide antifungal, shows potent *in vitro* activity against *L. prolificans* samples cultured in various regions, including the USA, Spain, Germany and Australia. [1]. In an Australian study by Biswas, [15] olorofim demonstrated superior *in vitro* efficacy in 30 *L. prolificans* isolates, with an MIC range of 0.125–0.5 μg/ml and a geometric mean MIC of 0.26 μg/ml, 23–80 times lower than those for triazole agents. The FORMULA-OLS trial (NCT03583164) is a Phase IIb study currently evaluating olorofim in adults >18 years with difficult-to-treat invasive fungal infections. [16].

In our case, the patient's isolate had an olorofim MIC of 0.125 μg/ml, suggesting potential *in vivo* efficacy. However, access to olorofim was not possible. At time of writing, there are no clinical trials currently evaluating the efficacy and safety of olorofim in young children, resulting in a lack of access to an important, potentially life- and limb-saving treatment option. This shortfall places children at a distinct and unfair disadvantage in accessing optimal treatments for drug-resistant infections. Children are often excluded from clinical trials of novel agents and between 2007 and 2017, only 24 out of the 17,495 paediatric trials registered on clinicaltrials.gov were for antifungal drugs. [17]. There is therefore an urgent need for enhanced paediatric antifungal research.

Achieving therapeutic voriconazole levels in young children is challenging due to age-related pharmacokinetic variability. Children under three often require higher doses to maintain serum concentrations within the narrow therapeutic window (1–5 mg/L) due to altered CYP2C19 activity. [18]. Drug levels >5 mg/L increase the risk of neurological and ocular toxicity, but these symptoms can occur even within a 'therapeutic' (1–5 mg/L) range. [19]. Risk factors for photosensitivity in our case included prolonged therapy resulting in a high cumulative dose, Caucasian ethnicity, and high potential for UV light exposure (living in Australia). [20]. This underscores the importance of close skin monitoring and proactive sun avoidance for all patients prescribed voriconazole, irrespective of serum levels.

Several adjunctive therapies may have contributed to our patient's successful outcome. Voriconazole-loaded polymethylmethacrylate (PMMA) Palacos® bone cement was used to achieve high local drug concentrations at infection sites. This delivery method was potentially advantageous given concerns about necrotic or poorly perfused osteoarticular tissue. While its utility is documented in adult *L. prolificans* bone infections [21,22], this approach has not been reported in

Table 2
Overview of case reports of invasive *L. prolificans* osteoarticular infections in children.

Year	Location	Author	Age (y)	Gender	Site of infection	Clinical details	Primary antifungal therapy	Reported adverse effects	Additional management	Outcomes
2024	USA	Pough [6]	12	M	Knee	Penetrating injury secondary to dog bite	Voriconazole, caspofungin and terbinafine	None reported	Debridement, intraarticular voriconazole instillation	Return to normal function 6 months of therapy
2024	Netherlands	Verbakel [7]	12	M	Knee	Deep laceration secondary to fall onto pot plant	Voriconazole and terbinafine	Photophobia, photosensitivity, brittle nails, myopathy, anorexia, anaemia, and osteoporosis	Debridement, joint irrigation with PHMB	Femoral fracture, 3 cm leg length discrepancy, residual pain and disability, after 13 months of therapy
2014	United Kingdom	Bhagavatula [8]	4	M	Ankle	Penetrating injury by thorn	Voriconazole and terbinafine	Hallucinations, nail discolouration, and skin rash	Radical debridement, removal of navicular bone and part of talar head	Return to normal function 6 months of therapy
2013	India	Matlani [9]	10	M	Knee	Fall from bicycle	Voriconazole	None reported	Surgical debridement, initially treated with antituberculous medication (misdiagnosed as TB)	Return to normal function after 6 months of therapy
2009	Australia	Kesson [10]	8	F	Pelvis, Hip	Multiple compound fractures from an accident	Voriconazole, terbinafine and miltefosine	Skin toxicity	Debridement, interferon-gamma	Residual limp but return to normal function, after 14 months of therapy
2003	Sweden	Studahl [11]	9	M	Knee	Penetration injury by hawthorn spike	Voriconazole	Skin depigmentation and nail onycholysis	Radical debridement and arthrodesis	Return to normal function after 17 months of therapy.
2003	USA	Steinbach [12]	5	M	Foot	Penetrating injury by metal nail	Voriconazole and caspofungin	Hallucinations	Debridement, joint irrigation with PHMB	Return to normal function after 1.5 months of therapy

paediatric cases. Irrigation with an antiseptic solution may have also reduced fungal bioburden within the joint. Prontosan® contains 0.1 % betaine, which disrupts biofilm, and 0.1 % polyhexanide (PHMB), a broad-spectrum antiseptic agent. Successful use of PHMB has been reported in immunocompetent paediatric patients with *L. prolificans* infections. [14,22]. Our report further supports its adjunctive role in this context.

In summary, we report a 3-year-old immunocompetent boy who developed a limb-threatening *Lomentospora prolificans* elbow infection after internal fixation for a closed fracture. Limb function was preserved and amputation avoided following successful treatment with aggressive surgical debridement, combination systemic antifungal therapy including voriconazole, terbinafine and micafungin, voriconazole-loaded bone cement and antiseptic joint irrigation. This case supports the need for multidisciplinary collaboration to manage fungal bone and joint infections in children. Accessing new antifungal drugs for children remains challenging. There is an urgent need for research in current and emerging paediatric antifungal therapies for difficult-to-treat infections.

Fig. 1; "Fig. 1. Serum voriconazole concentration over course of treatment".

CRediT authorship contribution statement

Niall Johnston: Writing – review & editing, Writing – original draft, Data curation. **Bradley Rockliff:** Writing – review & editing. **Robert Duguid:** Writing – review & editing. **Pamela Palasanthiran:** Writing – review & editing. **Adam W. Bartlett:** Writing – review & editing. **Phoebe CM. Willams:** Writing – review & editing. **Brendan J. McMullan:** Writing – review & editing, Conceptualization.

Conflict of interest

There are none.

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