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Case report

Chronic paronychia associated with fluconazole use in two pediatric patients with coccidioidomycosis

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ABSTRACT

Azoles are frequently used to treat systemic mycoses but have been associated with a number of adverse effects of the skin and skin appendages. Herein we describe two cases of chronic paronychia in pediatric patients receiving fluconazole for coccidioidomycosis. Their clinical characteristics are described, and the literature reviewed.

Introduction

Fluconazole, a triazole antifungal medication, is frequently employed in the southwestern United States for the treatment of coccidioidomycosis. Though usually well tolerated, it is known to cause mucocutaneous side effects including xerosis, cheilitis, and alopecia. We describe two cases in which patients on long term fluconazole therapy developed nail disorders, with resolution after cessation of antifungal therapy. To our knowledge, this is the first description of chronic paronychia due to fluconazole.

Case descriptions

Case 1: A 13-year-old male with nephrotic syndrome on corticosteroids and tacrolimus was diagnosed with pulmonary coccidioidomycosis and started on fluconazole 400 mg by mouth daily. Steroids were weaned and tacrolimus was continued. He had no prior history of paronychia and no history of trauma. Within weeks of starting the fluconazole, he developed xerosis of the lips as well as erythema, edema, and induration of the lateral nail folds of the bilateral great toes with serous discharge and crusts. These changes persisted despite oral cephalexin, topical corticosteroids, and surgical intervention by podiatry. Fluconazole therapy was stopped after 12 months as his pulmonary symptoms had resolved and *Coccidioides* IgG titers as measured by complement fixation (CF) had normalized. Shortly after discontinuing the fluconazole, the paronychia resolved. Two months later, he developed worsening nephritis requiring escalation of his steroid dose. During that time, a new right lower lobe infiltrate was found on chest radiograph and *Coccidioides* CF titer had increased to 1:4. He was restarted on fluconazole, and paronychia recurred in the same nails within weeks. He continued fluconazole due to elevated *Coccidioides* CF titer and persistent immune suppression, and his dose was decreased to 200 mg by mouth daily 17 months later, while his paronychia persisted. He continued at this dose for another 11 months, at which time fluconazole was stopped due to decreased immune suppression, negative *Coccidioides* CF titers, and normal chest films. His nails returned to normal within two weeks of discontinuation of fluconazole. He has not had any recurrences on long term follow-up (4 years).

Case 2: An 11-year-old girl with a history of allogeneic stem cell transplantation 3 years prior for acute myelogenous leukemia was evaluated for fever, fatigue, chest tightness, acute-on-chronic headaches, and erythema nodosum. A chest radiograph demonstrated a rounded opacity in the right upper lobe; *Coccidioides* species IgG was positive by enzyme immunoassay, and her CF titer was 1:8. Magnetic resonance imaging of the brain was negative, and a cerebrospinal fluid (CSF) examination revealed no cytochemical abnormalities. CSF *Coccidioides* CF titers were negative. She was started on fluconazole 400 mg by mouth daily, and her symptoms resolved in the weeks that followed. Three months into therapy, she developed erythema and mild desquamation of the nail folds on each of her toes, with eventual associated dystrophic changes of the toenails. There was no associated pain or loss of function, and the patient perceived minimal social impact after she

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began painting her toenails. She had no prior history of paronychia or trauma previously. Her paronychia persisted for the remainder of her two-year treatment course, resolving one month after discontinuation of fluconazole.

Discussion

Paronychia is characterized by inflammation of the nail fold skin. Acute paronychia is often caused by bacteria and responds to antibiotics and/or surgical management. Chronic paronychia occurs when inflammation lasts beyond six weeks, and often affects more than one digit. Though bacteria and fungi can be implicated in chronic paronychia, many cases represent an inflammatory response resulting from malignancy, autoimmune disease, or drug toxicity [1].

Many medications, including retinoids, chemotherapeutic agents, epidermal growth factor receptor inhibitors, tyrosine kinase inhibitors, and the HIV protease inhibitor indinavir have been associated with chronic paronychia. While the exact mechanism remains unknown, it is postulated that some drugs exert a retinoid-like effect, given their impact on other mucocutaneous sites, resulting in xerosis and alopecia, in addition to paronychia. Some drugs, such as indinavir, have been shown to increase concentrations of endogenous retinoids, but it is unclear if this is the cause of these side effects [2,3].

Fluconazole achieves high drug concentrations within nails which is a property useful in treating onychomycosis [4]. Additionally, fluconazole can hinder the activity of CYP-26A1, an enzyme involved in the metabolism of retinoic acid. In patients with certain hematologic malignancies whose treatment includes all-trans retinoic acid (ATRA), co-administration of fluconazole can increase concentrations of ATRA, resulting in increased adverse effects [5,6]. In a mouse model of fluconazole-induced alopecia, fluconazole affected metabolism of retinoic acid but did not lead to accumulation of retinoic acid in serum or skin. Although fluconazole may inhibit retinoic acid metabolism temporarily, prolonged exposure induces metabolism of retinoic acid such that the increase is only transient, making it less likely that this is the cause of retinoid-like side effects [7].

Medication-related chronic paronychia can be managed with discontinuation of the offending agent. However, this is not always feasible. In such instances, topical anti-inflammatory agents, including corticosteroids or tacrolimus ointment, may be of benefit [8].

Fluconazole is the treatment of choice for coccidioidomycosis, with a duration of therapy that far exceeds those of other common indications for the drug in the ambulatory setting, such as candida vulvovaginitis. Therefore, fluconazole adverse effects are more likely to be encountered in patients treated for coccidioidomycosis. There are no reports of fluconazole-associated chronic paronychia in the literature. However, fluconazole has been implicated in a fixed drug eruption of the nail matrix [9]. The differential diagnosis includes photo-onycholysis, wherein onycholysis is induced following receipt of an inciting agent in areas exposed to sunlight, which may be accompanied by skin photosensitivity [9]. This can occur with or without skin changes and has been reported in a child receiving voriconazole [10].

Currently, the mechanism by which fluconazole leads to mucocutaneous adverse effects is unknown. Chronic paronychia may be associated with long-term fluconazole use but resolves promptly with discontinuation of the drug. Additional study is needed to ascertain whether there is a causal relationship, and to elucidate its mechanism. Recognition of this and other fluconazole adverse events is of increasing importance given the effects of climate change in expanding the endemic area of *Coccidioides* species [11].

CRediT authorship contribution statement

Kathryn R. Matthias: Writing – review & editing. **Kareem Walid Shehab:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Nathan B. Price:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Emily S. Cormack:** Writing – review & editing.

Declaration of Competing Interest

Nathan B. Price, MD: Consulted for DSM-Firmenich; no relevant conflict of interest to disclose. Emily S. Cormack, PharmD: nothing to disclose. Kathryn R. Matthias, PharmD: nothing to disclose. Kareem W. Shehab, MD: nothing to disclose.

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References

[1] Relhan V, Goel K, Bansal S, Garg VK. Management of chronic paronychia. Indian J Dermatol 2014;59(1):15–20. https://doi.org/10.4103/0019-5154.123482.
[2] Garcia-Silva J, Almagro M, Peña-Penabad C, Fonseca E. Indinavir-induced retinoid-like effects: incidence, clinical features and management. Drug Saf 2002;25(14):993–1003. https://doi.org/10.2165/00002018-200225140-00002.
[3] Wollina U. Systemic drug-induced chronic paronychia and periungual pyogenic granuloma. Indian Dermatol Online J 2018;9(5):293–8. https://doi.org/10.4103%2Fidoj.IDOJ_133_18.
[4] Davies-Strickleton H, Cook J, Hannam S, et al. Assessment of the nail penetration of antifungal agents. PLoS One 2020;15(2):e0229414. https://doi.org/10.1371%2Fjournal.pone.0229414.
[5] Schwartz EL, Hallam S, Gallagher RE, Wiernik PH. Inhibition of all-trans-retinoic acid metabolism by fluconazole in vitro and in patients with acute promyelocytic leukemia. Biochem Pharm 1995;50(7):923–8. https://doi.org/10.1016/0006-2952(95)00213-j.
[6] Vanier KL, Mattiussi AJ, Johnston DL. Interaction of all-trans-retinoic acid with fluconazole in acute promyelocytic leukemia. J Pedia Hematol Oncol 2003;25(5):403–4. https://doi.org/10.1097/00043426-200305000-00010.
[7] Thompson 3rd GR, Krois CR, Affolter VK, et al. Examination of fluconazole-induced alopecia in an animal model and human cohort. Antimicrob Agents Chemother 2019;63(2):e01384-18. https://doi.org/10.1128/aac.01384-18.
[8] Relhan V, Bansai A. Acute and chronic paronychia revisited: a narrative review. J Cutan Aesthet Surg 2022;15(1):1–16 (Jan-Mar).
[9] Hernandez LE, Jadoo A, Morrison B. Recurrent fluconazole-induced fixed drug eruption of the digit with nail matrix involvement: a case report and review of the literature. Ski Appendage Disord 2023;9(6):457–60. https://doi.org/10.1159/000532112.
[10] Willis ZI, Boyd AS, Di Pentima MC. Phototoxicity, pseudoporphyria, and photo-onycholysis due to voriconazole in a pediatric patient with leukemia and invasive aspergillosis. J Pediatr Infect Dis Soc 2015;4(2):e22–4. https://doi.org/10.1093/jpids/piu065.
[11] Head JR, Sondermeyer-Cooksey G, Heaney AK, et al. Effects of precipitation, heat, and drought on incidence and expansion of coccidioidomycosis in western USA: a longitudinal surveillance study. Lancet Planet Health 2022;6(10):e793–803. https://doi.org/10.1016%2FS2542-5196(22)00202-9.