

## A case of green nail syndrome secondary to *P. aeruginosa* and *C. parapsilosis* treated with topical nadifloxacin and oral fluconazole in a 31-year-old Filipino female

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### ABSTRACT

**INTRODUCTION** *Pseudomonas aeruginosa* is an opportunistic, gram-negative bacillus that can contaminate skin or open wounds to cause skin infections that are historically difficult to manage. The pathogenesis of green nail syndrome (GNS) begins with hyperhydration (occlusion, sweating, maceration) or destruction (microtrauma, dermatitis) of the epidermis thus disrupting the physical barrier, leading to the colonization and proliferation of *P. aeruginosa*. This case explores the off-label use of nadifloxacin, a fluoroquinolone approved for acne and bacterial skin infections in some countries, to treat a case of GNS.

**CASE REPORT** This is a case of a 31-year-old Filipino female who presented with a four-month history of green discoloration of the lateral portion of the right thumbnail with a medical history of antiphospholipid antibody syndrome and rheumatoid arthritis. Clinical examination showed a dystrophic thumbnail with greenish discoloration, erythema and swelling around the base of the cuticle, and distal onycholysis. Laboratory findings revealed co-infection of *P. aeruginosa* and *Candida parapsilosis*. The patient was effectively treated with topical nadifloxacin and oral fluconazole.

**CONCLUSION** This case highlights the possibility of fungal and polymicrobial infections in GNS and suggests a novel, easy-to-use, and cost-effective alternative treatment to GNS secondary to *P. aeruginosa* in the form of topical nadifloxacin.

**KEYWORDS** green nail syndrome, nadifloxacin, *Candida parapsilosis*, *Pseudomonas aeruginosa*, onychomycosis

### INTRODUCTION

*Pseudomonas aeruginosa* is an opportunistic, gram-negative bacillus that contaminates skin or open wounds to cause skin infections that are difficult to manage. *Pseudomonas* nail infection presents with a triad of green discoloration of the nail plate, proximal paronychia, and distolateral onycholysis.<sup>1</sup> Risk factors include prolonged contact with a moist environment, history of trauma, immunocompromised state, frequent wet work, and a history of hyperhidrosis.<sup>1</sup>

This study explores the off-label use of nadifloxacin, a fluoroquinolone approved for acne and bacterial skin infections, to treat green nail syndrome (GNS). There are only a few published reports on treatment with this drug, proposing a novel, easy-to-use, and cost-effective alternative treatment to GNS secondary to *P. aeruginosa*.

### CASE SUMMARY

A 31-year-old Filipino female presented with a four-month history of green discoloration of the lateral portion of the right thumbnail which was aggravated by frequent wet work, manicures, and excessive palmar sweating. No new medications were applied. In the interim, the patient noted an increase in size of discoloration, affecting the entire nail, hence consult at our clinic. She was undergoing immunosuppressive treatment for antiphospholipid antibody syndrome (APAS) and rheumatoid arthritis (RA), which may have compromised her immune system. Clinical examination showed a dystrophic right thumbnail with greenish discoloration, erythema and swelling around the base of the cuticle, and distal onycholysis. Dermoscopy presented a bright yellow green discoloration (Figure 1). There was distal onycholysis and

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**Conflict of interest**

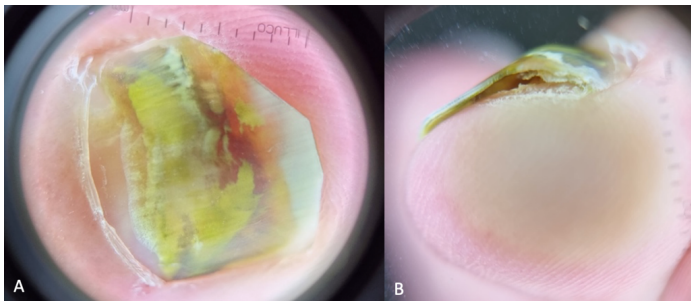
None

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**Table 1.** Laboratory results.

Gram Stain	
Pus cells/LPF	Rare
Epithelial cells/LPF	Moderate
Organisms/OIF	Gram positive cocci in pairs and in clusters - Few
Aerobic Culture and Sensitivity Test	Moderate growth of <i>Pseudomonas aeruginosa</i>
Interpretation	Antibiotic
Susceptibility	aztreonam, levofloxacin, tobramycin, doripenem, piperacillin-tazobactam, ceftazidime, cefepime, imipenem, meropenem, amikacin, gentamycin, ciprofloxacin
KOH wet mount	Positive for yeast cells
Fungal Culture	Positive for <i>Candida parapsilosis</i> after 48 hours of incubation
Interpretation	Antifungal
Susceptible	andulafungin, caspofungin, fluconazole, micafungin, voriconazole



**Figure 1.** Dermoscopy of the nail plate showed a bright yellow green discoloration of the nail plate with no visible blood vessels (A). Dermoscopy of the free edge demonstrated distal onycholysis and the presence of the pigment of the ventral side of the plate (B).

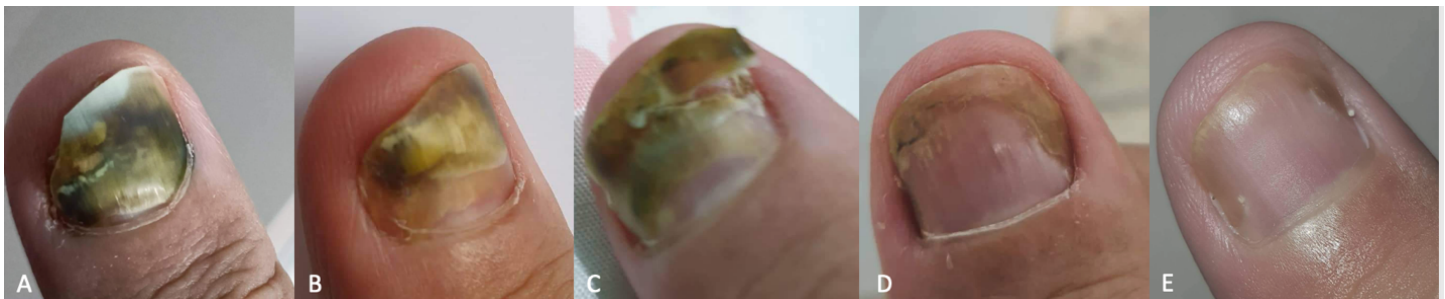
bright yellow green pigment on the ventral side of the nail plate (Figure 1).

With the clinical and dermoscopic findings, a primary impression of GNS was made. The following diagnostics were done: bacterial gram stain culture and sensitivity (GS/CS), 20% KOH, fungal culture and sensitivity of the affected nail as well as complete blood count, liver function tests, and creatinine level measurement.

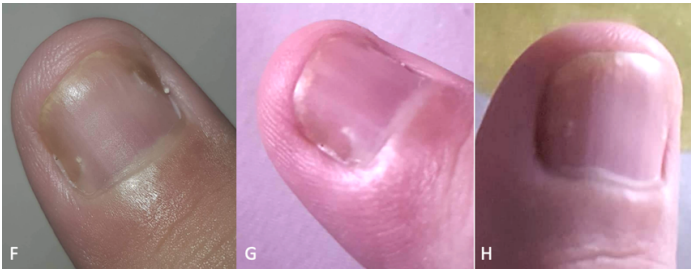
For the GS/CS, greenish discharge was collected on the distal nail bed beneath the free edge of the nail plate using a cotton pledget soaked in 0.9% normal saline solution. Results showed gram-positive cocci in pairs and in clusters, and bacterial culture had a moderate growth of *P. aeruginosa* (Table 1) as shown on Nutrient and MacConkey agar. The specimen for fungal culture was taken in the same manner, revealing growth of *C. parapsilosis* sensitive to fluconazole, andulafungin, caspofungin, micafungin, and voriconazole (Table 1). Clippings of the distal onycholytic nail were submitted for KOH which revealed yeast cells.

Nadifloxacin 1% cream was applied on the dorsal nail plate, free nail edge, and the spaces between the nail plate and distal nail bed at bedtime and occluded with clingwrap overnight on weeks 1 to 8. Oral fluconazole 150-300 mg/week was taken for 6 weeks. Figure 2 shows the patient's thumbnail at weeks 1 to 8 of treatment with nadifloxacin and Figure 3 illustrates weeks 8 to 19 with fluconazole. There was disappearance of the green discoloration after applying nadifloxacin (Figure 2) and further elimination of the yellow discoloration after intake of fluconazole (Figure 3), thus attaining complete clinical cure. The patient was advised to avoid excessive immersion in water, to keep nails clean and dry, and to trim nails at 4-week intervals until regrowth.

Twenty-four weeks after completion of treatment, the patient was instructed to undergo a repeat bacterial and



**Figure 2.** Weeks 1 to 8 of treatment with topical nadifloxacin. First consult (A), 2 weeks (B), 4 weeks (C), 6 weeks (D), 8 weeks (E).



**Figure 3.** Weeks 8 to 19 of fluconazole. Baseline (F), 13 weeks (G), 19 weeks (H).

fungal culture of the nail, however, she was not able to do so due to personal reasons. Although these should have been done to determine the definite cure rate, nadifloxacin has shown its efficacy in terms of partial clinical cure after eight (8) weeks, eliminating the greenish discoloration. Complete clinical cure resulted after the addition of fluconazole where the yellowish discoloration was eradicated.

## DISCUSSION

This is a case of a 31-year-old Filipino female who presented with a four-month history of green discoloration of the right thumbnail with a medical history of antiphospholipid antibody syndrome and rheumatoid arthritis. Clinical examination showed a dystrophic thumbnail with greenish discoloration, erythema and swelling around the base of the cuticle, and distal onycholysis. Laboratory findings revealed co-infection of *P. aeruginosa* and *C. parapsilosis* which were effectively treated with topical nadifloxacin and oral fluconazole.

The pathogenesis of GNS begins with hyperhydration (occlusion, sweating, maceration) or destruction (microtrauma, dermatitis) of the epidermis thus disrupting the physical barrier, leading to the colonization and proliferation of *P. aeruginosa*.<sup>1</sup> Rallis et al. enumerated the predisposing factors for GNS which are onycholysis, onychotillomania, microtrauma, chronic paronychia, chronic exposure to water, soaps or detergents, associated nail disorders, and an immunocompromised state.<sup>2</sup> The patient is a housewife who engaged in frequent wet work and weekly manicures which caused nail trauma. She was undergoing immunosuppressive treatment for APAS and RA, which may have compromised her immune system.

*P. aeruginosa* facilitates the spread of infection by producing collagenase, elastase, phospholipase, heat-stable thermolysin, vascular permeability factor, and fibrolysin.<sup>1</sup>

The bacteria digests keratin which explains the organism's ability to invade the nail plate. The greenish hue is due to pyocyanin and pyoverdine that accumulate as *P. aeruginosa* is metabolized.<sup>1</sup>

There are no published guidelines and clinical trials for treating GNS.<sup>1</sup> Therapies consist of topical antiseptics such as diluted acetic acid or sodium hypochlorite and oral antibiotics. Oral antibiotics such as ciprofloxacin are considered if topical antiseptics are unsuccessful, but they are not the first choice. The bacterial biofilm is approximately 1000 times less sensitive to antibiotics than isolated bacteria of the same species and the nail is not in contact with the nail bed so the antibiotic cannot reach the biofilm.<sup>3</sup> Topical antibiotics have shown success, wherein 21 patients were successfully treated with 0.3% gentamycin administered nightly for 12 weeks.<sup>4</sup> However, clinicians are wary that these are unlikely to adequately treat the infection and may lead to antibiotic resistance.<sup>1</sup>

While antibiotics proved to be effective, research shows increasing resistance to *P. aeruginosa*.<sup>5</sup> Hanberger et al. found that in five European countries, ciprofloxacin and gentamycin showed the highest incidence of resistance (37% resistant to ciprofloxacin in Portuguese ICUs and 46% resistant to gentamycin in French ICUs).<sup>5</sup> Thus, there is a need for novel strategies to treatment.

Topical nadifloxacin 1% cream is approved for the management of acne vulgaris and surgical site infections.<sup>6</sup> It has broad spectrum activity against gram-positive (including MRSA), gram-negative, and anaerobic bacteria, making this a promising treatment for GNS.<sup>6</sup> Due to its mechanism of action (binding to bacterial DNA gyrase and topoisomerase IV enzymes, inhibition of nor-A efflux pump, survival in acidic pH, anti-MRSA activity, and biofilms penetration), it has shown a very low chance of developing resistance.<sup>6</sup> Two (2) HIV-positive patients with pseudomonas nail infection of three (3) weeks duration were successfully treated with nadifloxacin, applied daily on affected nails and observed complete clearance within six (6) weeks.<sup>2</sup> Similarly, Müller et al. reported success with the treatment of two (2) immunocompetent patients with GNS by applying nadifloxacin.<sup>7</sup> For the first case, nadifloxacin was applied daily on the nail plate for six (6) weeks.<sup>7</sup> The co-infection with *C. parapsilosis* was treated with itraconazole 100 mg twice daily on weeks 1 and 5, demonstrating cure within 24 weeks.<sup>7</sup> For the second case, nadifloxacin was applied daily on the nail plate for six (6) weeks.<sup>7</sup> The nail plate was treated within 16 weeks of treatment.<sup>7</sup>

It is crucial to consider that polymicrobial and fungal infections may occur simultaneously, therefore, the identification of the etiology is imperative for appropriate treatment. In a study by Forouzan et al., the researchers concluded that while bacterial etiologies are common, fungal and polymicrobial infections may be more widespread than published literature suggests.<sup>8</sup> Ohn et al. found that GNS was frequently associated with concomitant onychomycosis and speculated that onychomycosis is a predisposing factor to GNS because the nail spaces beneath the lateral folds are ideal for the growth of *P. aeruginosa*.<sup>9</sup> This study was prudent in requesting for the necessary laboratory tests, thus, clinicians must wisely identify the infectious agents involved when faced with a case of GNS.

Fungal culture revealed a co-infection with *C. parapsilosis*. Studies show that *Candida* spp. were the most frequently isolated pathogens in onychomycosis and *C. parapsilosis* exhibits low phospholipase, proteinase, and biofilm formation activities.<sup>10</sup> This confirms the need to perform antifungal susceptibility testing of yeasts from patients with onychomycosis. Based on the susceptibility test (Table

1), the patient was given fluconazole at 150 mg/cap per week for 12 weeks achieving partial clinical cure with nadifloxacin as seen from the disappearance of the green discoloration. According to Ghannoum, et al., “Fluconazole is used in the treatment of onychomycosis in adults at a weekly dose of 150 to 450 mg for 3 to 6 months for finger and toenail onychomycosis, respectively.”<sup>3</sup> Treatment with fluconazole cleared the yellow discoloration achieving complete clinical cure.

This case emphasizes the importance of appropriate work-up to diagnose possible co-infections in GNS and proposes topical nadifloxacin as an effective treatment modality. Further research is recommended to strengthen its effectiveness.

## CONCLUSION

While GNS is rare, it is imperative to do appropriate work-up to diagnose possible co-infection to initiate appropriate treatment. This study highlights the possibility of fungal and polymicrobial infections in GNS, and suggests a novel, easy-to-use, and cost-effective alternative treatment to GNS secondary to *P. aeruginosa* in the form of topical nadifloxacin.

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