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Case report

Primary cutaneous nocardiosis caused by *Nocardia nova* with possible Apremilast contribution

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ABSTRACT

Primary cutaneous nocardiosis accounts for 5–8 % of all nocardiosis cases and represents a diagnostic dilemma among immunocompetent and immunocompromised hosts. Herein, we present a case of a 30-year-old male with history of psoriasis with recent addition of Apremilast. Patient received intralesional triamcinolone injections for psoriatic plaques on the hands and abdomen prior to traveling to warm climate vacation. While on vacation, patient developed hand swelling and painful, red nodules on the dorsal hands and abdomen, sites where he received intralesional injections. Patient was empirically given doxycycline, but continued to develop new nodules. An abdominal lesion was biopsied for H&E and tissue culture. Tissue culture revealed beaded gram-positive rods identified as *Nocardia nova* by MALDI-TOF. Patient was switched to trimethoprim-sulfamethoxazole with significant improvement. This case represents an atypical primary cutaneous nocardiosis with *Nocardia nova* most likely in the setting of intralesional steroid injections and possible contribution of Apremilast.

Introduction

Primary cutaneous nocardiosis accounts for about 5–8 % of all nocardiosis cases and may present with 4 clinical forms: superficial skin infection, lymphocutaneous infection, mycetoma, or disseminated infection with skin involvement [1–3]. *Nocardia nova* has been implicated in the development of all 4 forms; however, 80 % cases of primary cutaneous nocardiosis are caused by *Nocardia brasiliensis* [4–11]. Other clinical manifestations of nocardiosis include lung involvement (39 %) and a disseminated picture (32 %) [12–14]. Nocardia is a ubiquitous, saprophytic, gram-positive, partially acid-fast bacteria found worldwide in the soil, decayed organic matter, water, and air. Southwestern and Southeastern United States harbor most of nocardiosis cases [7,8,15]. Human infection occurs by direct inoculation or inhalation; it is predominantly pathogenic to the immunocompromised people [7].

Herein we present the first case report of primary cutaneous nocardiosis due to *Nocardia nova* in a patient on Apremilast. Apremilast is a selective PDE-4 inhibitor that downregulates TNF-alpha, which is important for the control of nocardial infections.

Case report

A 30-year-old male with psoriasis and psoriatic arthritis on recent regimen addition of Apremilast 6 months ago, presented with pain and erythematous nodules on the dorsum of his hands, trunk, abdomen, shoulders, and back after returning from a warm climate vacation (Fig. 1*A*). Three days prior to his travel, he received intralesional triamcinolone acetonide (Kenalog-40) injections to his psoriatic lesions without complications. After a full body massage, on day 9 after Kenalog-40, he developed erythematous and painful lesions around the areas where he received injections. He reported swimming in the hotel and ocean, but did not participate in any hiking or fresh-water swimming. Upon initial presentation, the patient was afebrile and well-appearing. Laboratory work-up revealed leukocytosis of 13.2 $\times$ 10^3 cells/microliter, segmented neutrophils: 76 %. The patient was diagnosed with cellulitis and prescribed a ten-day course of doxycycline 100 mg twice daily.

Ten days later, the patient presented to the emergency department with aggravation of lesions swelling, induration and pain despite completing the doxycycline course (Fig. 1*B*). He remained well-appearing and afebrile. Laboratory work-up was

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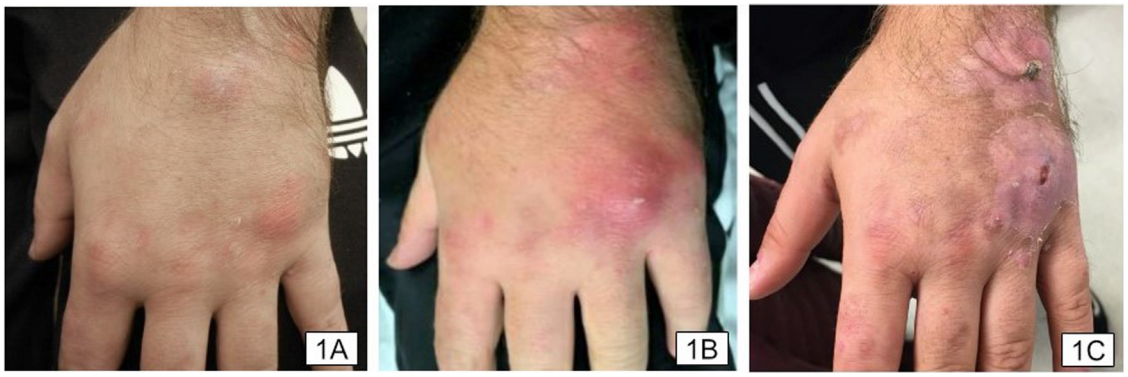

Fig. 1. Clinical pictures. ***A***, Erythematous nodules on dorsum of the left hand, initial presentation. ***B***, Same lesions after 10 days of doxycycline, second presentation. ***C***, Same lesions after trimethoprime-sulfamethoxazole, resolution.

unremarkable with the exception of leukocytosis with white blood cell count of 17.5 $\times$ 10^3 cells/microliter, segmented neutrophils: 81 %. A 2 mm x 2 mm punch biopsy of an abdomen lesion was obtained and demonstrated perivascular infiltrate of lymphocytes as well as an interstitial neutrophilic infiltrate suggestive of infection (Fig. 2*A*–*C*). Gram stain, periodic acid-Schiff stain, acid-fast bacilli (Ziehl–Neelsen) stain, and Wade-Fite stain were negative for organisms. Ultimately, tissue culture grew gram-positive branching rods (Fig. 2*D*), which was identified as *Nocardia nova* by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS). Two sets of blood cultures were negative. Given that nocardiosis usually affects immuno-compromised patients and may result in pulmonary involvement and disseminated infection [16–20], the patient underwent HIV testing, chest X-ray and head computed tomography scan – all were negative. He was started on sulfamethoxazole-trimethoprim DS 1 tablet three times a day with significant clinical improvement (Fig. 1*C*).

Discussion

The diagnosis of cutaneous nocardiosis is challenging given the rarity of this entity and its non-specific clinical features that resemble other bacterial and fungal skin infections. Skin lesions due to *Nocardia* species are frequently misdiagnosed as staphylococcal or streptococcal soft tissue infections, atypical mycobacteria infection, sporotrichosis, furunculosis or other non-infectious diseases including rheumatoid nodules, Sweet syndrome, and

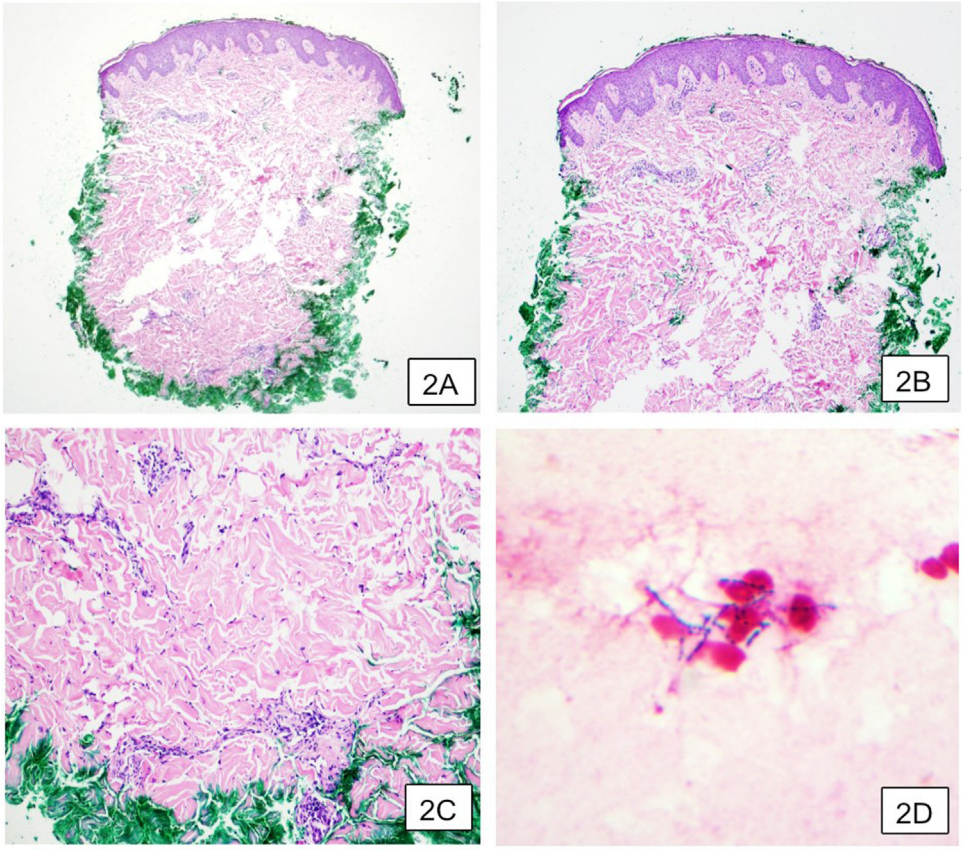

Fig. 2. Skin biopsy of the abdominal lesion, histomorphology. ***A***, Non-specific perivascular inflammation (H&E, 2×). ***B***-***C***, Perivascular lymphocytic and interstitial neutrophilic infiltrate (H&E, 10× and 20×). ***D***, Tissue culture, gram-positive branching rods (Gram stain, 40×).

panniculitis. Further, the diagnosis of nocardiosis is often delayed due to slow bacterial growth in culture, difficulty of bacterial identification on Gram stain without appropriate molecular studies confirmation [21–24], and non-specific pathological findings on biopsy. Nocardia requires a minimum of 48–72 h to grow before colonies are evident, and in some cases can take as long as 14 days to appear [15].

Nocardia infection primarily affects immunocompromised patients, including patients with bone marrow and solid organ transplants, renal insufficiency, HIV/AIDS, and hematologic malignancy. A high index of suspicion is needed in these patients as the infection can be associated with a high mortality rate and can spread to brain [16,25,26]. In our case, the patient grew an uncommon cutaneous pathogen – *Nocardia nova (N. nova)*. *N. nova* is more commonly identified in patients with bone marrow and solid organ transplants [27,28] who develop disseminated disease (with secondary cutaneous involvement) [29]. Most reported cases of *N. nova* infection show severe pulmonary disease and/or brain abscesses in immunocompromised patients [30,31], where a lesser number of pulmonary and central nervous system complications are reported in immunocompetent hosts [32,33].

Our patient had a new regimen addition of Apremilast for his psoriatic arthritis for the last 6 months and a long history of intralesional steroid injections without history of cutaneous infections. Torres T. et al. described the Apremilast is an oral, small-molecule phosphodiesterase 4 inhibitor that works intracellularly by blocking the degradation of cyclic adenosine 3′,5′-monophosphate, resulting in increased intracellular cyclic adenosine 3′,5′-monophosphate levels in phosphodiesterase 4-expressing cells. This inhibition results in the reduced expression of proinflammatory mediators including TNF-alpha and an increased expression of anti-inflammatory mediators [34]. Given that TNF-alpha is an important proinflammatory mediator involved in the clearance and immune response against infection from *Nocardia* spp., it is possible that this patient's use of Apremilast may contributed to the development of cutaneous nocardiosis infection [35,36]. However, Nocardia has been reported rarely among patients on anti-TNF agents [37,38]. In fact, Apremilast is considered the lowest risk category and one of the recommended medications in individuals with LTBI (a surrogate marker for individuals at high risk for infections while receiving TNF-alpha blockers) by American Association of Dermatology [39]. Further, phase III and IV clinical trials of Otezla have failed to demonstrate increased risk of cutaneous infections, and a very small number of systemic infections have been reported [40–42]. On the other hand, there is a well-established association showing association of nocardiosis with immunosuppressants intake, in particular topical and oral corticosteroids [18,36,43,44]. Our patient received intralesional triamcinolone acetate injections right before his trip to Aruba that possibly contributed to his disease in the way of local immunosuppression that theoretically could provide the direct inoculation of *Nocardia* spp. from the environment.

This patient was treated with trimethoprim-sulfamethoxazole until his lesions improved. While TMP-SMX is typically effective in the treatment of cutaneous nocardiosis, there is an increasing rate of resistance to folate biosynthesis pathway inhibitors in *Nocardia* spp. Recently, Metha H. et al described pathways of resistance to the folate biosynthesis inhibitors involving mutations in dihydrofolate reductase (DHFR), dihydropteroate synthase (DHPS) (FolP), and a homolog of DHPS (DHPS2 or FolP2) that was previously considered "non-functional" [45].

To our knowledge, this is the first case of primary cutaneous nocardiosis caused by *N. nova* in a patient after intralesional corticosteroids injections with possible anti-inflammatory effect of systemic PDE4 inhibitor.

Conclusions

Primary cutaneous nocardiosis in the immunocompetent host is an uncommon clinical scenario. History of intralesional injection at the site of infection should prompt investigation for atypical organisms, including *Nocardia* spp., especially if the patient fails to respond to anti-staphylococcal therapy. Lesional biopsy with tissue culture is essential for identification of the underlying organism so that appropriate therapy can be initiated. The predominant and more likely cause of this case is pointing towards intralesional steroid injections. However, the impact of systemic PDE4 inhibitor, Apremilast, and its anti-inflammatory effect on the etiology of primary cutaneous nocardiosis remains questionable and more case reports needed.

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Nothing to declare.

Consent

No consent needed.

Author contribution

Volha Lenskaya: writing-original draft preparation, editing, reviewing; **Vincent DeChavez**: writing, reviewing, editing, data collection, formal analysis; **Bridget Kaufman**: data and picture collection, editing, resources, supervision; **Daniel Caplivski**: project administration, supervision, coordination, data collection.

Declaration of Competing Interest

All authors report no declarations of interest and no funding source.

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