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FOCUS ON FUNGAL INFECTIONS

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February 16-20, 2018
San Diego, California

International Investigative Dermatology (IID) Annual Meeting
May 16-19, 2018
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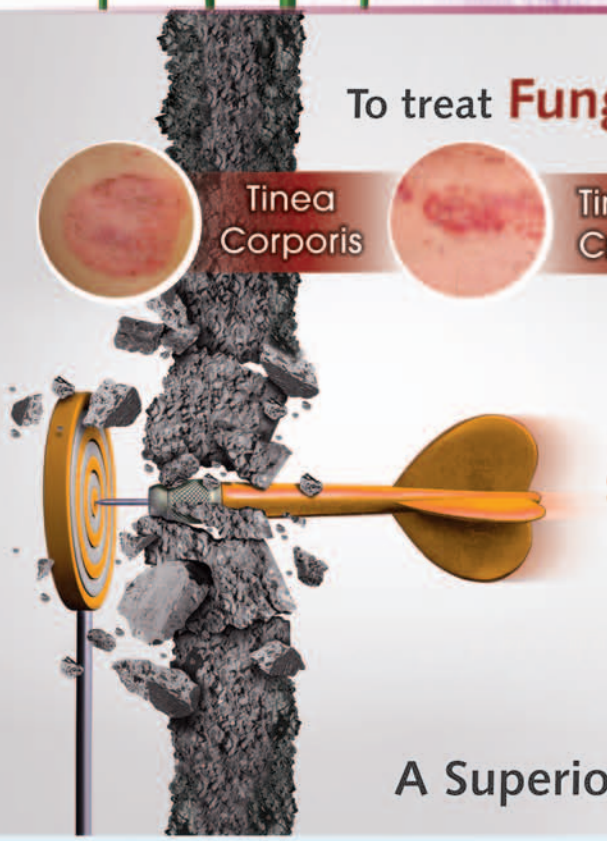

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Mixed nondermatophyte and dermatophyte toenail onychomycosis versus pure dermatophyte onychomycosis: An insight

Salakshna N , Bunyaratavej S, Matthapan L, Lertrujiwanit K, Leeyaphan C

A number of mixed onychomycosis infections caused by dermatophyte (DMPs) and nondermatophyte mold (NDMs) coinfection are on rise and commonly reported in clinics. However, the role of NDMs is not well-defined when coinfection occurs with DMPs. This study set forth to investigate the clinical manifestations and treatment outcomes of mixed onychomycosis infection, and the factors affecting those outcomes. A cohort study was conducted involving 121 patients diagnosed with DMPs and/or NDMs toenail onychomycosis at Thailand's largest national tertiary center during the 2008 to 2016 study period. Cox's regression was used to determine how each factor affected time to cure.

The outcomes of the study were:

- The study reported 38.8% of mixed infections
- No marked variation was reported in the clinical presentations of mixed infections and those caused by pure organisms

No marked variation is seen in the clinical presentations of mixed infections and those caused by pure organisms in onychomycosis

- Factors associated with complete cure were pure DMPs, immunocompetent status, and thickness of the affected nail of ≤2 mm (adjusted HR:2.26, 3.03, and 2.58; p=.043, .013, and .013, respectively).
- Longer median time to complete cure was reported for mixed infections than DMPs (4.27 vs. 1.79 years; p=.002), and a significantly longer mean duration of oral treatment than pure DMPs (10.55±8.68 vs. 7.17±6.20 months, respectively; p=.041).

It is difficult to differentiate clinically mixed onychomycosis infections from infections caused by pure organisms. However, mixed infections are more challenging to treat than pure DMPs. Hence, mixed infections should be recognized as a distinct type of onychomycosis.

Clinical utility of direct microscopic examination in diagnosis of Malassezia folliculitis

Tsai YC

Potassium hydroxide (KOH) examinations with Parker ink and Chicago sky blue stain are useful for identifying Malassezia and facilitating rapid diagnosis of pityriasis versicolor. However, there are only few studies reporting their use in Malassezia folliculitis diagnosis. A study was concluded to investigate whether direct microscopic examinations with inks reduce biopsies and medical costs for Malassezia folliculitis diagnosis. The study involved a total of 321 patients with Malassezia folliculitis from 2008 to 2016, and segregated them into direct microscopy (249 cases) and biopsy groups (72 cases). The number of annual biopsies, average cost of diagnosis, clinical symptoms and signs, and treatment outcomes were evaluated.

The outcomes of the study were:

- The introduction of direct microscopic examinations led to an increased in diagnosis of Malassezia folliculitis from 14 to 52/year
- The study also reported a decrease in the mean cost of diagnosis from 3411 to 161 NTD/case
- Compared with the biopsy group, the direct microscopy group reported fewer patients with a history of ineffective oral antibiotic treatment (19.7% vs 38.9%, p< 0.001).

Hence, use of direct microscopic examination, especially with Chicago sky blue stain resulted in rapid and accurate Malassezia folliculitis diagnoses, thereby curtailing unnecessary need of biopsies and medical costs.

Direct microscopic examination, especially with Chicago sky blue stain resulted in rapid and accurate Malassezia folliculitis diagnoses, thereby curtailing unnecessary need of biopsies and medical costs

Causes underneath persistent dermatophytosis

Sharma V, Bhari N, Xess I, Mahajan R.

Relapse in the patients with Tinea corporis and or cruris is very common. In addition, there are cases in which patients show incomplete response to treatment. A study was conducted to determine the minimum inhibitory concentration (MIC) of the commonly used antifungal drugs in such cases and to identify predisposing factors. The study included patients from the out-patient department with Tinea corporis and or cruris persisting for more than one year. Detailed history was noted including age and sex, duration of disease, seasonal variation, risk factors like personal history of diabetes mellitus, alcoholism, atopy and family history of dermatophytic infections. Skin scrapings were collected for the microscopic evaluation and fungal culture. Antifungal susceptibility was performed using the broth microdilution assay according to Clinical Laboratory Standards Institute (CLSI) approved standard M38-A2 guidelines suggested for molds.

The results showed that 89 (62 male and 27 female) patients with a clinical diagnosis of persistent dermatophytosis were enrolled in the study.

- The mean age was 30.62±11.82 years (10-63 years).
- Mean duration of illness was 22.61± 19.16 months (range 6-108 mo).
- Allergic rhinitis was present in 24 cases, atopic dermatitis and urticaria in 1 case each.
- Family history of similar illness was recorded 28.09% cases.
- History of regular alcohol intake was noted in 20 cases and smoking in 15 cases.
- KOH scrapings for dermatophyte were positive in 71.91% cases.
- The culture on Sabouraud's dextrose agar was found positive in 42.69% of them.
- The most common organisms isolated was *Trichophyton mentagrophytes* in 42.10% cases, followed by *Trichophyton interdigitale* in 21.05%, *Trichophyton tonsurans* in 7.89%, *Trichophyton rubrum* in 2.63%, uncharacterized Microsporum species in 2.63% and Trichophyton species in 23.68% cases.
- On drug culture sensitivity, MIC 50 of itraconazole 0.03µg/ml, terbinafine 0.5µg/ml, griseofulvin 0.5 µg/ml and amphotericin 0.125 µg/ml and MIC 90 of itraconazole 0.06µg/ml, terbinafine 1µg/ml, griseofulvin 1 µg/ml and amphotericin 0.25 µg/ml was noted.

These results inferred that persistent dermatophytosis was associated with atopy, regular alcohol intake, smoking and family history of dermatophytosis. In addition, there was diminished sensitivity of dermatophytes to terbinafine and griseofulvin in contrast to the maintained sensitivity to itraconazole.

Table 1: The most common organisms isolated from patients with Tinea corporis and cruris

Organisms isolated	Percentage
Trichophyton mentagrophytes	42.10%
Trichophyton interdigitale	21.05%
Trichophyton tonsurans	7.89%
Trichophyton rubrum	2.63%
Uncharacterized Microsporum species	2.63%
Uncharacterized Trichophyton species	23.68%

Persistent dermatophytosis was associated with atopy, regular alcohol intake, smoking and family history of dermatophytosis

Evaluating the duration of treatment effect of 1064 nm neodymium-doped yttrium aluminum garnet (Nd:YAG) laser on the patients with onychomycosis

Suh DH, Ahn HJ, Kang IH, Jung KH, Lee SJ, Shin MK

Management of onychomycosis using Neodymium-doped yttrium aluminum garnet (Nd:YAG) laser has been reported to be clinically effective. A study was done to evaluate the duration of efficacy of 1064 nm Nd:YAG laser for onychomycosis. In this study, the investigators retrospectively reviewed one-year follow-up records of patients with onychomycosis who were treated with Nd:YAG from February 2014 to November 2015. A total of 36 patients who underwent 3 or 4 laser treatments at 4-week intervals were investigated for the duration of therapeutic effect. The results of the study were as following:

- 94.4% patients showed the therapeutic effect for several months.
- 58.3% patients who showed excellent response were all remained well for average of 6.7 months after discontinuing laser therapy.
- Out of 41.7% patients who were moderate to poor response, 86.7% patients remained in their previous state for average of 2.2 months, 13.3% patients were worsened after 1 to 2 months of cessation of laser treatment.

Thus, it could be inferred that the use of Nd:YAG laser treatment could effect for maintenance status in onychomycosis patients.

The use of Nd:YAG laser treatment could be effective as maintenance therapy in onychomycosis patients

Chemical nail avulsion as an alternative treatment for nail dystrophy

Leung AJ, Yang SS, MeiQi ML, Pan JY.

Chemical nail avulsion is a lesser-known therapeutic modality for nail pathologies. In this treatment approach, the dystrophic nail is trimmed, pared and subsequently occluded with 40% urea to dissolve nail keratin over a week. It is a seemingly viable alternative to long-term antifungals or painful surgical procedures.

The present study evaluated the efficacy and safety of chemical nail avulsion as a treatment modality in patients presenting with nail pathologies. It comprised of a retrospective analysis of chemical nail avulsions performed in the National Skin Centre, Singapore, from 2013 to 2015. The indication, site and outcome of the nail avulsion was assessed, along with the number of therapeutic cycles required, the presence of any adverse effects and patient satisfaction. A total of 157 patients, with mean age 49.8 (ranging from 3 - 90) years, were assessed amongst whom 78 were men and 79 women. The majority of patients were of Chinese

Chemical nail avulsion was well tolerated and effective in improving nail dystrophy, with high patient satisfaction

ethnicity- 109 (69.4%), followed by Indians 24 (15.3%), Malays 5 (3.2%) and others. The main indication was onychomycosis with residual nail dystrophy post-treatment (80, 51.0%). Others indications included onychodystrophy (27, 17.2%), traumatic nail injuries (19,12.1%), ingrown (15, 9.5%) and pincer toenails (12, 7.6%). Less frequent indications included chronic paronychia, melanonychia, onychogryphosis and onychomadesis. Most avulsions were performed on toenails (118, 75.2%) as compared to fingernails (32, 20.4%), with 8 patients having both finger and toenail involvement. 126 patients (80.3%) had one treatment cycle, while the remainder required 2-4 cycles.

The study analysis reported significant improvement in 53 (33.8%) patients and partial improvement in 90 (57.3%) patients while 14 patients (8.9%) had no improvement of their nail dystrophy with chemical nail avulsion. The procedure was well tolerated, with 6 (3.8%) patients reporting a pain score of 5-6 out of 10, while 1 patient (0.6%) had cellulitis requiring oral antibiotics. 2 (1.3%) patients developed irritant contact dermatitis to urea. Of the 68 patients who expressed feedback, 56 (82.4%) reported a good outcome, 5 (8.9%) reported a high satisfaction while 7 (10.3%) patients were dissatisfied due to lack of response to the avulsion. Thereby, it was concluded that chemical nail avulsion is a promising alternative therapy with most patients experiencing good improvement. Its safety was evidenced by the few patients who expressed mild discomfort, with no reported major side effects.

Pityriasis versicolor atypica: A difficult diagnosis

Salazar-Nievas M, Moreno-Suarez F, Aceituno-Madera P

Pityriasis versicolor is a superficial mycosis of the skin caused by various species of Malassezia, which are dimorphic lipophilic yeasts and a part of the cutaneous microbiota. The most frequent topography is the trunk wherein the clinical presentation consists of distinguishing plaques with fine scales on the surface, which may be hypochromic, hyperchromic or erythematous. It is usually asymptomatic, but chronic and recurrent in nature.

The genus Malassezia, from its description, has long caused confusion and controversy. For years the Malassezia-Pityrosporum complex, termed Malassezia furfur, represented the mycelial phase of the lipophilic yeast that causes pityriasis versicolor; whereas the terms Pityrosporum ovale and orbiculare were reserved for the two morphological types of the yeast phase. Currently the genus Pityrosporum is synonymous with Malassezia and seven species of Malassezia are recognised as causative agents of pityriasis versicolor, namely: M. furfur, M. pachidermatis, M. sympodialis, M. globosa, M. slooffiae, M. restricta and M. obtusa.

In furtherance of the above facts, a case of a 55-year-old woman was presented who complained of scaly lesions on the neck and face since one month. She had been treated by her doctor with topical corticosteroids without any improvement. The injuries had increased in number since then and the patient also reported mild pruritus. A biopsy compatible with tinea versicolor was thus

At least 7 species of Malassezia are recognized as causative agents in pityriasis versicolor; thus its lesions, which frequently affect the trunk area, can also present at atypical sites such as the face and neck

performed. Treatment with oral itraconazole was subsequently instituted which resulted in complete resolution of the lesions. The case highlights the diagnostic difficulty posed with atypical pityriasis versicolor. Although pityriasis versicolor can be easily diagnosed clinically in the presence of risk factors and concomitant presence of hypo or hyperpigmented maculas, with their characteristic distribution and desquamation, the cases with atypical presentation may warrant further investigations. As in the aforementioned case, the lesions were located exclusively on the face and neck, a rare area, and the trunk was not affected, thus necessitating a biopsy. An increased understanding of atypical presentations of pityriasis versicolor, such as those on the face and neck, can therefore forego need for skin biopsy.

Features of mixed onychomycosis infections and diagnostic role of feet culture

Bunyaratavej S, Limphoka P, Leeyaphan C, Salakshna N.

The number of mixed onychomycosis infections caused by dermatophyte (DMPs) and non-dermatophytes (NDMs) continues to increase. Infections caused by DMPs are diagnosed on the basis of mycological laboratory investigations while those caused by NDMs have multiple other diagnostic criteria. Few evidences have demonstrated the relationship between foot and nail infections caused by fungi. The current study aimed at evaluating the prevalence of mixed infection of nails previously diagnosed as onychomycosis caused by DMPs. Additionally, the duration for clinical and mycological cure as well as the relationship between concomitant fungal foot infection and onychomycosis was also assessed.

A total of 83 nails which were earlier diagnosed with infections caused by DMPs with/without fungal foot infection and treated with oral antifungal drugs during the period between 2008 and 2016 were included in the study. Repeat fungal culture of feet along with nails was performed, and infections in which NDMs were also identified were called mixed infections. Results divulged the following:

- Mean age of the patients was 62±13 years and about 54.2% of them were females
- About 42.2% cases of mixed onychomycosis infections were reported which were earlier diagnosed as DMP infections
- Median time to clinical cure was significantly longer in cases of mixed infections than DMP infections (4.27 vs. 1.77 years, p= 0.003)
- Similarly, median time to mycological cure was significantly longer in mixed infections as compared to DMPs (2.59 vs. 0.70 years, p=0.000)
- Following antifungal therapy, 57.8% cases were identified as pure DMPs while 42.2% were mixed infections
- All cases with pure DMPs presented with mycological feet culture along with nail culture
- In mixed infections group, fungal feet culture revealed NDMs in 71.4% cases whereas nail culture showed only DMPs (p=0.000).

Feet culture is an important tool to diagnose mixed infections, and hence it should be performed simultaneously with nail culture in cases of onychomycosis

The study findings suggest that mixed onychomycosis infections result in a longer time to cure than isolated DMPs. Furthermore, feet culture is an important tool to diagnose mixed infections, and hence it should be performed simultaneously with nail culture in cases of onychomycosis.

Evaluation of the onychoscopic patterns of onychomycosis and traumatic onychodystrophy

Pinheiro RP, Domingues TD, de Sousa VC, et al.

Onychomycosis (OM) and traumatic onychodystrophy (OD) commonly results in toenail dystrophy. There are differences in the treatment and prognosis of both conditions. Hence, early diagnosis of both disorders is essential. Onychoscopy is considered to be a useful tool. However, studies elucidating the onychoscopic findings of OM and OD are limited. In order to address this issue, the current study was conducted with an aim to identify and distinguish the onychoscopic patterns of OM and OD.

The study participants included a total of 192 patients presenting with onychodystrohy of at least one toenail. These patients were subjected to physical, onychoscopic and mycological examination (direct KOH 40% and fungal culture). Few cases were selected for conducting histological examination of collected nail clippings. On the basis of these results, patients were diagnosed with OM or OD. Additionally, onychoscopy was performed and an association between onychoscopic patterns and final diagnosis of OM or OD were evaluated. Results demonstrated the following:

- OM and OD were diagnosed in 110 and 82 patients, respectively
- The onychoscopic patterns that were identified include: regular macular (n=23), irregular macular with spikes (n=62), macular with grayish margin (n=4), longitudinal lines (n=16), distal pulverized (subungual hyperkeratosis) (n=16), total hazy homogeneous background (HHB) (n=22), partial HHB (n=15), focal macular (n=2) and distal fine line pattern (n=15)
- Dermoscopy changes were not classified into any of these forms in a total of 17 patients
- The irregular macular and the distal pulverized patterns were found to be significantly associated with OM ($p < 0.001$)
- Additionally, a statistically significant association was observed between OD diagnosis and 4 onychoscopic patterns i.e. regular macular, total HHB, partial HHB and the fine line pattern ($p < 0.005$).

Hence, the study findings showed that OM and OD have distinctive onychoscopic patterns whose detection can aid in the diagnosis.

Detection of the distinctive onychoscopic patterns of onychomycosis and traumatic onychodystrophy can aid in the diagnosis of these conditions

Potential therapy and molecular characteristics of a multidrug-resistant dermatophtye

M Sinha, S Sadhasivam, A Bhattacharyya, S Ghosh, S Saini, H Singh, S Gupta, A Gupta, K Sardana and S Ghosh.

Dermatophytes are the most common cause of superficial fungal infections in humans. Trichophyton spp. is commonly associated with superficial infections in immunocompetent people, but in immunocompromised patients it can cause even deep or systemic infections. These invasive fungal infections pose major management problems for the clinicians as the number of non-responders to the conventional first line therapy are increasing. As little evidence is available on drug resistance in Trichophyton spp., a comprehensive study was undertaken. Trichophyton spp. was isolated from tinea patients and microbiological and molecular biological assays were employed to study the antifungal resistance patterns in these isolates. Recalcitrant stains were differentiated from wild types using genomic and proteomic techniques. Majority of the isolates were Trichophyton mentagrophytes with increased fluconazole and terbinafine MIC in contrast to the standard strain. KA-01 was an isolate which exhibited increased MIC for

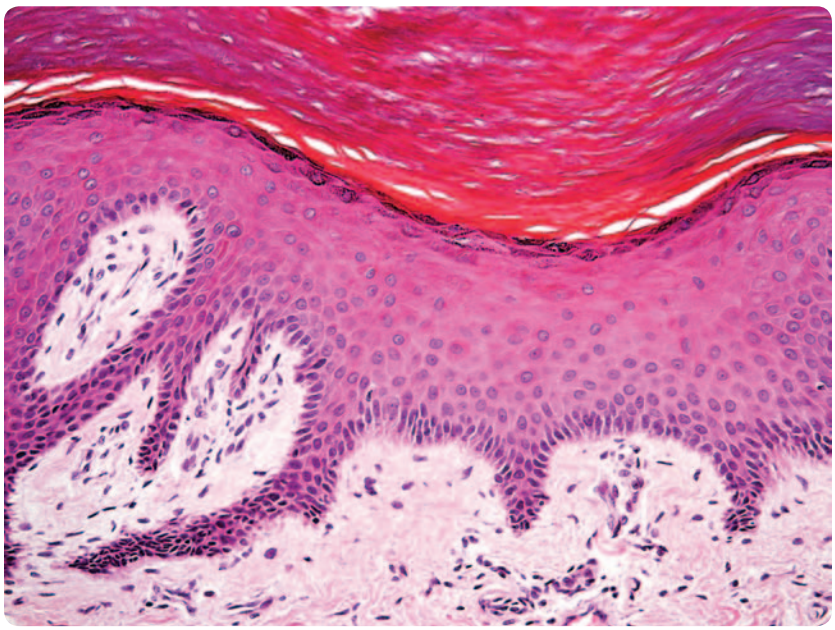
Lipid based topical therapies are effective in treating clinically non-responsive dermatophytic infections with increased drug resistance

multiple azoles and allylamines. On further evaluation, the azole resistance of KA-01 could be attributed to the variations in protein expression whereas terbinafine resistance was due to a point mutation in squalene epoxidase gene. This strain was remarkably sensitivity to lipid based formulations, which proved to be a therapeutic benefit as against marketed formulations of terbinafine or azoles. Hence, it was concluded that lipid based topical therapies are effective for clinical non-responders infected with dermatophytes displaying pan antifungal resistance.

Effect of Trichophyton rubrum infection on reconstructed human epidermis

E Faway, L Cambier, B Mignon, C Lambert de Rouvroit, Y Poumay

Superficial fungal infections account for nearly 25% of the global skin mycoses, making dermatophytic infections one of the most common types of infective diseases worldwide. The effects of dermatophytosis on epidermal barrier functions and cell responses in keratinocytes remain uncertain. Hence, an in vitro model of reconstructed human epidermis (RHE) infected by arthroconidia of Trichophyton rubrum was examined. A sudden loss in the barrier after four days of infection was observed with dye permeation and assays of trans-epithelial electrical resistance. This sudden loss in barrier function could be attributed to disorganized tight junctions, since simultaneous internalization of claudin-1 immunoreactivity was monitored. The fungal hyphae were seen invading the stratum corneum upto the granular layer of RHE via the intercellular spaces during electron microscopy. Also on the fourth day of infection, there was a progressive increase in pro-inflammatory cytokines (IL-1a, IL-1b, TNFa, IL-8, TSLP) and antimicrobial peptides (b-defensin-2, b-defensin-3, S100A7) released by keratinocytes. The synchronicity in the events of barrier disruption and keratinocyte activation called for an investigation towards prospective causal relationship. While assessing the potential role of p38 MAPK activation in outcome of fungal infection, the use of inhibitor PD169316 indicated that fungal homolog of p38 might be involved in growth of arthroconidia. It was observed by SEM that RHE treated with PD169316 were protected against invasion and growth of T. rubrum colonies on Sabouraud agar. Hence, it was concluded that fungal p38 MAPK signaling was a potential target to counteract dermatophytosis.



Fungal p38 MAPK signaling is a potential target to prevent dermatophytic infections

A method of increasing diagnostic sensitivity of onychomycosis with a 6-week nail-clipping collection

Yau B, Magee J, Holland T, Sinclair R, Spelman L.

Onychomycosis or tinea unguium, the fungal infection of nail, has been reported in up to 30% of the population. Currently, the diagnostic methods for this condition include examination of nail clippings with laboratory procedures like – direct microscopic examination (DME) using potassium hydrochloride staining (KOH), histopathology with Periodic Schiff (PAS) staining and mycological culture. A single time point examination of the fungal nail clippings is often non-diagnostic and the sensitivity of these methods has been found to be quite low. Recently, more advanced and accurate methods have been developed such as Molecular/DNA-based techniques, but

these methods are not cost-effective and have poor accessibility. It is suggested to use at least two methods of examination for confirmation of nail penetrance and identification of the fungal species. In this study, patients will be asked to collect nail clippings over a 6-week period (at least 3 collections) with an aim to increase the sensitivity of this diagnostic technique. The results of this method will be compared to a single isolated nail clipping collection at the surgery. It is being speculated that with this technique, there will be an increased identification rate of cultures or microscopy measuring by Chi-square or Fischer's exact tests between collection groups and examination methods.

A single time point examination of the fungal nail clippings is often non-diagnostic and the sensitivity of these methods has been found to be quite low

Severe fungal tracheitis on secukinumab: A case report

Vu M, Dolianitis C, Varigos G, Nicolopoulos J.

Secukinumab, a highly selective monoclonal antibody, acts by targeting the pro-inflammatory cytokine interleukin (IL)-17A. IL-17A plays an important role in the pathogenesis of chronic plaque psoriasis and is also a key component of the immune system's response to extracellular pathogens such as fungi. Although it is well-established that mild to moderate fungal infections are common on secukinumab treatment, there has not been any report on occurrence of severe life threatening infections. This is the case report of the first known presentation of fungal tracheitis resulting in acute respiratory distress in a patient with chronic plaque psoriasis on secukinumab, entailing the treatment to be discontinued. This case underscores that serious life threatening opportunistic fungal infections can occur during treatment with secukinumab with the need for immediate referral for diagnosis and suitable management.

Secukinumab, a highly selective monoclonal antibody, acts by targeting the pro-inflammatory cytokine interleukin-17A

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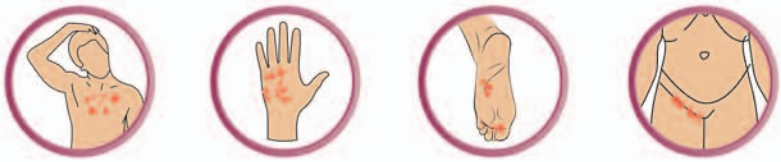

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