CASE REPORT

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A Case of Onychomycosis Due to *Aspergillus flavus* in all Fingernails and Toenails of an Immunocompromised Patient and Healing with 5-Fluorouracil Chemotherapy

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ABSTRACT Onychomycosis is a common disorder which is characterized with thickness and discoloration of nails. It accounts for the half of the nail disorders. Diabetic patients are particularly susceptible to fungal infections due to modifications that occur in their immunological system. Studies detected an increased risk among all three major groups of organisms that can cause onychomycosis in diabetic patients: dermatophytes, yeasts, and non-dermatophyte molds . We present a case of onychomycosis due to *Aspergillus flavus* 41-year-old male patient with diabetes mellitus and pancreas cancer because of the improvement of nails after chemotherapy with 5-Fluorouracil.

Keywords: Onychomycosis; aspergillus flavus; diabetes mellitus; malignant disease; cancer chemotherapy; 5-fluouracil

Onychomycosis is the general name for a mycotic nail infection caused by dermatophytes, yeasts, and nondermatophyte molds. The prevalence of onychomycosis has been reported to be 2-30% and has increased in recent years.[1] Onychomycosis is a highly prevalent infection worldwide with a range between 2% and 30%, corresponding to 50% of nail diseases and 30% of superficial mycoses. The classification is as follows; distal subungual, proximal subungual, candidal, white superficial and dystrophic onychomycosis. The aetiology of this condition is multifactorial. Old age, toenail deformities, onychodystrophy, diabetes mellitus, psoriasis, cellular immunity disorders, genetic predisposition, peripheral arterial circulatory disorder, other circulatory disorders, nail and nail fold microtrauma, and immunosuppression should be considered as risk factors for onychomycosis.[2] Three types of fungus cause onychomycosis: The majortiy of toenail infections are caused by dermatophytes. *Trichophyton rubrum* is the most frequently isolated microorganism from toe nails of patients with onychomycosis. Yeasts are true fungi that lack hyphae and cannot therefore be classified as moulds. *Candida albicans* is the yeast most commonly isolated (5.6%). Yeasts typically affect fingernails rather than toenails. Moulds (nondermatophytic fungi) are more rarely involved and the most commonly isolated saprophytic mould is *Aspergillus species.*[3]

Aspergillus species are ubiquitous environmental molds frequently isolated from soil, air, water, and vegetation. Over the recent years, onychomycosis caused by different Aspergillus species is increasing, evidenced

by case reports and epidemiological studies.[4-6] The incidence rate of onychomycosis caused by *Aspergillus* spp. has been described as 2.6% to 6.1%.[7]

The purpose of this work was to observe and characterize an opportunistic onychomycosis caused by *Aspergillus flavus*, an mould described as causative agent of onychomycosis, and to report the sensitivity of *Aspergillus flavus* to 5-Fluorouracil.

CASE REPORT

41-year-old male was admitted to the dermatology outpatient clinic of our hospital with complaints of deformity and thickening of the handnails and toenails for a duration of approximately one year. On dermatological examination, of bilateral handnails and toenails, subungual hyperkeratosis in varying degrees and yellow-brown discoloration were observed (Figure 1).

The patient complained of extreme fatigue and weight loss and he described pain on the right upper abdomen. He had a past medical history of diabetes mellitus for a duration 8 years and thickening of his nails has for a year. He was taking antidiabetic drugs. His family history consisted of diabetes mellitus and coronary artery disease.

A direct mycological examination was performed with 10% potassium hydroxide preparation (KOH), and fungal structures such as arthrospores and hyphae were considered as conferring positivity in the direct examination.The patient's fingernail specimen was planted in appropriate media. After a certain period of time the cultures of the fingernail yielded greenish-yellow to olive colored, velvety to woolly colonies . Microscopic examination of the lactophenol cotton blue stained colonies indicated long conidiophores with spherical to elongate vesicles surrounded by uniseriate

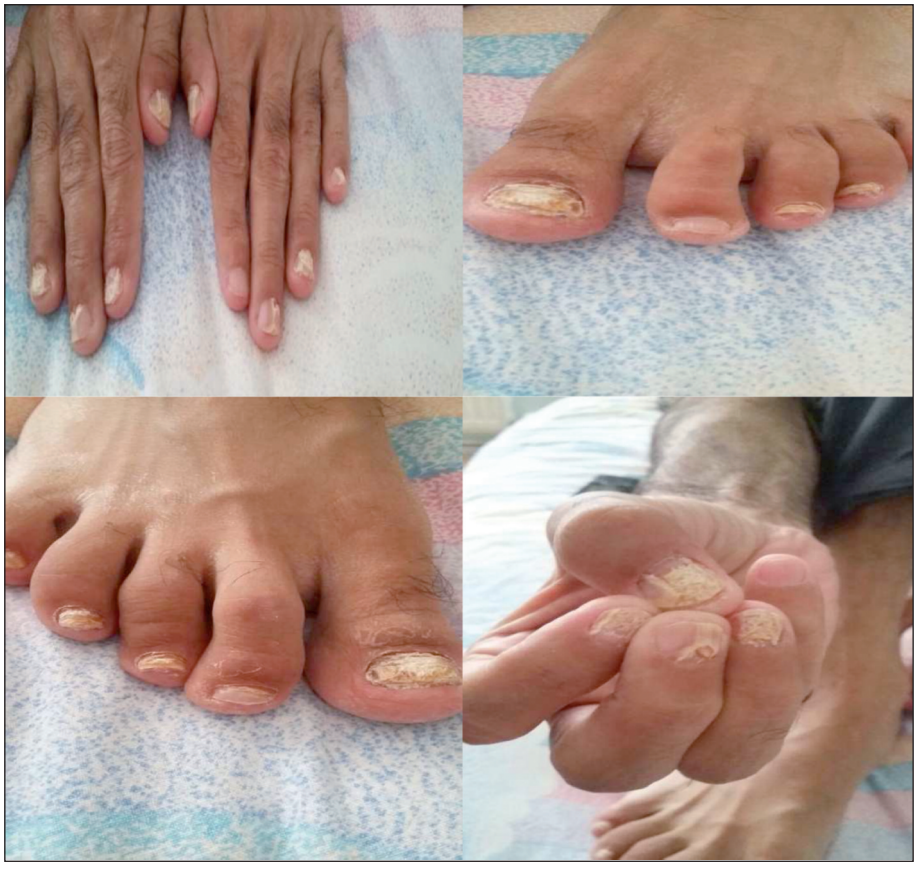

FIGURE 1: Brown discoloration and total dystrophy on the thumb fingernails and toe nails.

phialides and conidia were globose to ellipsoidal. Colony forming characteristics were compatible with *Aspergillus flavus* and subsequently the necessary procedures were performed on the breeding colony and identified on VITEK-MALDI-TOF MS device. Both MALDI-TOF MS and microscopy results were evaluated together with the features of breeding colony that yielded the identification of *Aspergillus flavus* (Figure 2).

Laboratory studies were obtained. Complete blood count, erythrocyte sedimentation rate, liver and kidney function tests, blood glucose, pancreas amylase, lipase levels, carcinoembryonic antigen (CEA) and lactate dehydrogenase (LDH) were within normal limits. Hemoglobine was detected as 11.78 g/dl (N 13.5-17.5 g/dl), carbohydrate antigen was detected as 19-9 (Ca 19-9) 9019 U/ml (N 0-35 U/ml).

On clinical examination a tender mass was observed in the upper right abdomen. The patient's upper and lower abdomen computerized tomography (CT) was performed. CT scan of the abdomen revealed a mass of 4.2 *3 cm in diameter in the pancreas. Sclerotic metastasis was detected in the anterior corpus of the lumbar vertebra 2. Fine needle aspiration biopsy was performed. Biopsy was compatible with pancreas end-stage adenocarcinoma.

The patient was diagnosed with pancreatic cancer and 6 cycles of chemotherapy treatment were started. In this case, the patient was given chemotherapy with Oxaliplatin 130 mg, Irinotecan 280 mg, Fluorouracil 3790 mg and Folinic Acid 630 mg. The treatment was determined to be every 28 days. The Ca 19-9 value at the end of 2nd cycle was 1339.8. Improvement was observed in the nails during chemotherapy. At the end of the 4th month, proximal clearing of all nails and thinning of the nail plates were observed (Figure 3).

Topical antifungal lotion treatment was planned after the end of systemic chemotherapy.

DISCUSSION

Onychomycosis is an infection of the nail plate by fungal microorganisms. This disease occurs via fungal invasion of the nail. Over the development course of the infection, there is initial colonisation with subsequent invasion of the nail bed and plate that cause changes in the nail colour, texture, and shape. Onychomycosis is a common nail ailment associated with significant physical and psychological morbidity.[8] A higher prevalence has been reported in men, individuals over 60 years of age, patients with immunosuppressive diseases, such as human immunodeficiency virus (HIV) infection or immunological defects, diabetics, and patients with peripheral vascular disease and malignant disease. Onychomycosis is a well known complication of diabetes mellitus. About one third of diabetic patients are affected.[9] Studies have shown that diabetic patients are at a higher risk of contracting onychomycosis compared to non-diabetics It is caused by dermatophytes, nondermatophytic molds, and yeasts.[10]

Although it is reported that dermatophytes and yeasts are the most common cause for onycomycosis, nondermatophyte molds (NDM) such as *Aspergillus* spp., *Fusarium* spp., *Acremonium* spp., and *Scopulariopsis* spp., were also found as the most common pathogens for onychomycosis in patients with diabetes.[11] In the past, these molds have been regarded as saprophytic or opportunistic fungi and have been basically ignored. Recently, as a

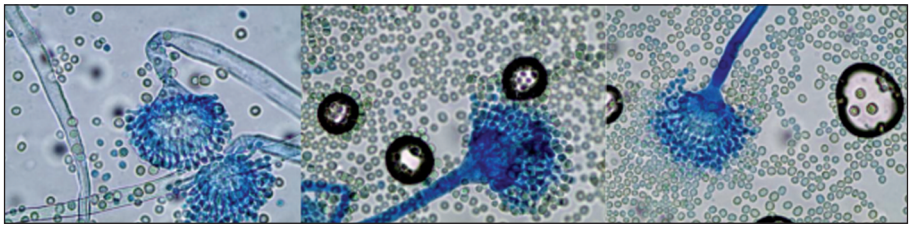

FIGURE 2: Slide culture shows conidial heads each consisting of a vesicle and radially arranged conidia.

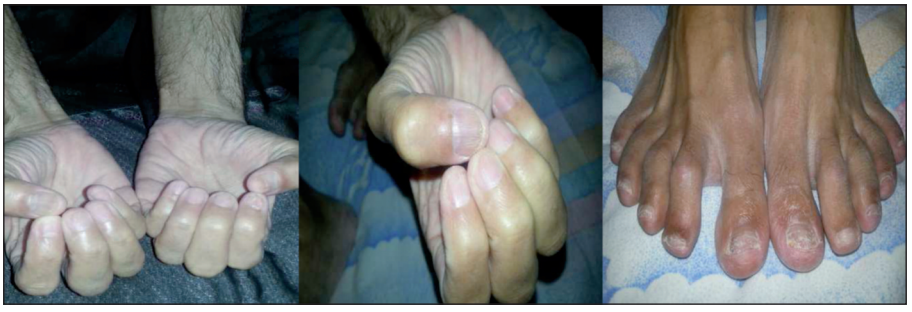

FIGURE 3: Patient's nails after 4 doses of chemotherapy.

consequence of an increase in the number of cases of immunodepression and environmental changes, more attention has been given to this wide, but generally non-pathogenic group of fungi.[11]

Diabetes, peripheral vascular disease, trauma and immunosuppression are the most important underlying conditions in onychomycosis due to Aspergillus species. Wijesuriya et al. showed that Aspergillus species was the most common pathogen isolated from toenail infection in diabetic patients.[12,13] Diabetic patients are more susceptible to fungal infections in toenails due to diminished blood circulation, increased thickness of the nail plate, decreased the growth rate of the nail, and poor foot hygiene. In a study conducted in Iran, it was found that *Aspergillus flavus* was the most common species in patients with onychomycosis.[14] Noguchi showed that *Aspergillus flavus* was the most common fungal pathogen isolated from hand nail in diabetic patients.[15]

It is not possible for a dermatologist to diagnose aspergillus onychomycosis just by looking at the affected nail. The proof of the ability of the organism to produce the nail infection depends on the direct demonstration of the fungus in the infected nail and its culture on artificial media. MALDI-TOF MS (Matrix- assisted laser desorption iozination- time of flight mass spectrometry) is a new and sensitive method for identification of microorganisms. This method is based revealing of microorganisms protein profile with ionization of protein structure and these ionized mass pass through the electrical and/or magnetic field. Profiles which were obtained from microorganisms compared with database of system thus identification is made by this way. In comparison with conventional identification methods that rely on biochemical tests and require long incubation procedures, identification by MALDI-TOF MS of microorganism is reliable and much quicker.[16] The diagnosis of non-dermatophyte mold onychomycosis requires stringent criteria than that of dermatophytes. Because both KOH and fungal culture false negative results or long incubation time required, we used MALDI-TOF as the cofirmation test.

Skin manifestations are a reflection of many of the internal diseases. Internal malignancies may give rise to a number of cutaneous manifestations through their immunological, metabolic, and metastatic consequences. Ductal adenocarcinoma, which represents the most common type of exocrine carcinoma, accounts for approximately 85% of pancreatic tumors.[17] Pancreatic ductal cell adenocarcinoma is showing an increasing incidence in the developed countries. Factors associated with the higher incidence of pancreatic ductal cell adenocarcinoma are smoking, obesity, diet, diabetes mellitus, chronic pancreatitis, and genetic predisposition in approximately 5-10% of patients.[18,19] Treatment varies depending on the severity of nail changes, the organism involved, and concerns about adverse effects and drug interactions. Systemic antifungals are the most effective treatment but topical therapy is less effective.[20] 5- Flucytosine is a antifungal drug and also a antimetabolite agent which acts by blocking nucleic asid synthesis. Flucytosine enters the fungal cell via cytosine permease; thus, flucytosine is metabolized to 5-fluorouracil within fungal organisms. The 5-fluoro uracil is extensively incorporated into fungal RNA

and inhibits synthesis of both DNA and RNA. The result is unbalanced growth and death of the fungal organism. Although the exact mode of action is unknown, it has been proposed that flucytosine acts directly on fungal organisms by competitive inhibition of purine and pyrimidine uptake and indirectly by intracellular metabolism to 5-fluorouracil. Flucytosine enters the fungal cell via cytosine permease; thus, flucytosine is metabolized to 5-fluorouracil within fungal organisms.[21] It also appears to be an inhibitor of fungal thymidylate synthase and Candida and Aspergillus species are susceptible to Flucytosine. In our patient, we think that 5-Fluorasil used for chemotherapy blocks the enzyme of thymidylate synthetase and inhibits DNA and RNA synthesis of *Aspergillus flavus*.

There are many studies in the literature that fungal species are susceptible to flucytosine. Cunha et al. reported that onychomycosis caused by the yeast *Rhodotorula mucilaginosa* was identified in a patient nail and have shown that this species is sensitive to 5-Flucytosine in an antifungal susceptibility test.[22] On the contrary Buzina showed that all species of Aspergillus investigated so far are resistant against the antifungals fluconazole and 5-fluorocytosine.[23] Verweij et al study provides evidence that the majority of clinical *Aspergillus fumigatus* isolates are susceptible to flucytosine.[24]

Nondermatophyte moulds (NDM) are the rare cause of onychomycosis. In our patient, malignancy and diabetes mellitus probably by suppressing the immune system may have played a role for the development of onychomycosis in all nails. We presented the patient with chemotherapy with 5-Fluorouracil and improvement in nail onychomycosis.

Informed Consent: *The authors certify that they have obtained all appropriate patient consent forms.*

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Yesim Akpınar Kara;* ***Design:*** *Yesim Akpınar Kara;* ***Control/Supervision:*** *Yesim Akpınar Kara;* ***Data Collection and/or Processing:*** *Yesim Akpınar Kara;* ***Analysis and/or Interpretation:*** *Yesim Akpınar Kara;* ***Literature Review:*** *Yesim Akpınar Kara;* ***Writing the Article:*** *Yesim Akpınar Kara;* ***Critical Review:*** *Yesim Akpınar Kara;* ***References and Fundings:*** *Yesim Akpınar Kara, Fatma Gülru Erdoğan, Derya Çöloğlu;* ***Materials:*** *Yesim Akpınar Kara.*

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