“EFFECT OF ASPERGILLUS SPECIES ON SKIN INFECTION”

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ABSTRACT:
We present such a case, manifested by ulceration on skin due to A. niger, which remained undiagnosed for a prolonged period. Although the patient had associated severe fungal infection. Recurrence of the lesion occurred despite repeated anti-fungal therapies. Anti fungal testing was done based on the broth dilution (M-38A, AIIMS, INDIA) method. The culture isolate was found to be sensitive to fluconazole and amphotericin B. Continuation of antifungal therapy improved the symptoms, reducing the size of the lesion.

Key words: Aspergillus niger, Skin infection, ulcer, Aspergillus lentulus., Broth dilution.

1. INTRODUCTION:
Approximately 200 000 species of moulds have been identified so far, where only a small group of around 200 may present a threat to human health. Fungi from Aspergillus species are among the moulds considered to be most pathogenic. They also constitute the group of most pathogenic moulds most frequently isolated from the environment. Over 250 types of this species are known; about 50 of them were precisely described before the year 2000 (Klich, 2009). Pathogenicity, due to their toxicity, was also documented in other species: Aspergillus fumigatus, Aspergillus flavus, Aspergillus ochraceus, Aspergillus niger, Aspergillus versicolor, Aspergillus parasiticus. Aspergillus nidulans, Aspergillus ustus, Aspergillus glaucus, Aspergillus clavatus, Aspergillus sydowii and Aspergillus terreus. Their taxonomic identification is still an open topic because of their morphological variability and ability to produce metabolites; new species which exhibit adverse health effects to humans are constantly being detected. Aspergillus lentulus is one of the recently detected species of considerable clinical importance; it reveals similarity to Aspergillus fumigatus, one of the most pathogenic fungus for humans (Balajee et al., 2005). Table 1 presents the classification of species of fungi pathogenic to humans from the Aspergillus species. The list has been created by the authors of “Atlas Grzybów Chorobotwórczych Człowieka” ("Atlas of Fungi Pathogenic to Humans") (Krzyściak et al., 2011). Those natural products, poisonous to humans and animals, are created as
the result of a secondary metabolic process of fungi, when grown on organic substrates. Chemical structure of these metabolites varies; however, they are largely of small molecular mass, which conditions their varied toxic characteristics. So far over 400 metabolites produced by moulds have been identified from different genus of fungi: *Aspergillus* sp., *Penicillium* sp., *Fusarium* sp., *Alternaria* sp. *Trichothecium* sp. Or *Stachybotrys* sp. Secondary metabolites of fungi from *Aspergillus* species are: ochratoxin A, aflatoxin B1, aflatoxins G1 and M1, trichothecenes, sterigmatosystin, patulins, gliotoxins or cyclopiazonic acid. It usually occurs as a complication of severe debilitating illnesses and is seen in patients suffering from malignancies, tuberculosis, silicosis and diabetes. It also occurs in patients who are receiving long-term corticosteroids, antibiotics or cytotoxic drugs and are in immunocompromised states with neutropenia. Cutaneous aspergillosis is a rare form of a locally invasive disease. It may be primary, involving the sites of skin injury following intravenous cannulation, trauma, occlusive dressing, burns or surgery. Secondary cutaneous lesions may result from widespread haematogenous seeding of the skin. In immunocompromised patients, primary cutaneous aspergillosis is most commonly caused by *A. β avus* and *A. fumigatus*.[2,3] However, this cutaneous lesion is rarely associated with *Aspergillus niger*.

Table 1 presents the classification of species of fungi

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2. MATERIAL AND METHODS:

2.1 Case Study: A 30-year-old man presented with a large non-healing painful ulcer over an erythematous plaque on the upper arm, just below the shoulder, since the last 10 years. The ulcer had gradually increased in size to 20 cm 20 cm (Fig. 1). It was characterized by a punched-out margin, indurated base and erythematous granulation tissue, with purulent discharge. The ulcer developed from an asymptomatic, painless nodule of about 4 cm to 5 cm in size. There was no history of trauma, invasive procedure, discharging sinus or grains at that site. An empirical diagnosis of cutaneous tuberculosis was made and he received anti-tubercular treatment for two years without much benefit. He then presented to our hospital where a punch biopsy from the ulcer edge revealed necrotizing granulomatous inß ammation with septate fungal hyphae showing acute angle branching,
suggestive of aspergillosis. He was treated with oral ketoconazole 200 mg twice daily along with oral drops of saturated solution of potassium iodide (SSKI, 45 drops thrice daily). He took the treatment regularly for six months. This led to near complete healing of the ulcer and about 50% reduction in the size of plaque. He then took treatment, albeit irregularly, for another two months, and there was near complete resolution of the ulcer and inß ammation. The patient remained asymptomatic for the next one year except for the presence of a scar. Then, slowly an ulcerated plaque formed within the scar on the arm and a new ulcer appeared in theleft groin. The recurrence was treated with a combination of itraconazole and potassium iodide for six months. The ulcer responded well to therapy, but once again recurred after he discontinued treatment. The sequence of nearly 80 . 90% resolution followed by a recrudescence occurred ß ve more times despite various combination treatments including ketoconazole, potassium iodide and itraconazole. The patient revealed that he stopped treatment on his own after some improvement because he could not afford the medication. He never took the treatment for a complete duration, as advised. During the course of illness, he was found to have concomitant paucibacillary leprosy (pure neuritic type, which does not present with primary skin lesions) and received treatment with paucibacillary multidrug therapy (PB-MDT) for six months. He developed extensive tinea corporis, which cleared after therapy with griseofulvin 250 mg once daily orally and ketoconazole 200 mg twice daily, for one year. There were no other associated medical illnesses and his general health remained good during the entire period of follow-up. The patient was found to be HIV negative with CD4 count 965 cells/ml. Repeated attempts to isolate the causative organisms by fungal culture during his previous hospital admissions had been unsuccessful. During the current hospital stay, a punch biopsy sample was taken from the ulcer edge as a base for histopathological and microbiological examinations. Haematoxylin and eosin staining of the tissue showed several acute angle branching septate hyphae and giant cells with dense lymphocytic inß ltrate in the upper and lower dermis (Fig. 2A, 2B). A direct KOH mount revealed the presence of thin hyaline septate hyphae with acute angle branching (Fig. 3). The Gram stain showed the absence of bacteria and the Ziehl Neelsen stain was negative for acid fast bacilli. The biopsy material was inoculated in sabouraud dextrose agar (SDA) with and without cycloheximide in duplicate and incubated at 37 cm and 25cm, respectively. After 72 hours, all tubes were seen with cottony white mycelium growth, which was soon covered with abundant black spores. No bacterial growth was detected in the culture. Microscopic characterization of the fungal isolate was carried out by preparing a lactophenol cotton blue mount from the growth. They mostly consisted of erect conidiophores. The conidiophores terminated in a vesicle covered with phialides (biseriate). The secondary phialide bore chains of globose conidia that were dark and covered the entire surface. The conidial head was large, black and radiate. The fungal isolate was conÞ rmed to be Aspergillus niger by the above-mentioned features. We also performed antifungal susceptibility testing for ß uconazole and amphotericin B using the broth dilution method (M-38A,NCCLS, USA). The isolate was sensitive to both the drugs and showed inhibition of growth for amphotericin B and ß uconazole at the lowest minimum inhibitory concentration (MIC).

Figure 1: Non-healing painful ulcer
3. RESULT AND DISCUSSION:

Aspergillus species is the most ubiquitous fungi seen in soil, water and decaying vegetations. It affects the lungs, central nervous system, naso-orbital area, skin and sometimes, it may be disseminated. Cutaneous aspergillosis is mostly caused by *A. ß avus, A. fumigatus*, and rarely, by *A. niger*. Clinically, the lesion is characterized by macules, papules, plaques or haemorrhagic bullae, which may progress into necrotic ulcers that are covered with a heavy black eschar. The condition usually occurs in association with immunocompromised patients. Our patient was not having a compromised immune status.

However, cutaneous aspergillosis is not uncommon in immunocompetent patients. Burik *et al.* found 6% of lesions caused by *A. niger* in patients not infected with HIV. Prompt recognition and appropriate treatment is necessary to prevent adverse outcomes. Treatment of cutaneous aspergillosis included a combination of surgical debridement and multi-drug antifungal chemotherapy. In view of extensive tissue involvement, debridement was not done in this case, as it would have led to a larger defect. Itraconazole was used as the first line of therapy in localized lesions.

4. CONCLUSION:

Ajith *et al.* reported a case of cutaneous aspergillosis which showed complete clearance of the lesion with oral itraconazole treatment. It had to be changed to intravenous amphotericin B if the lesion worsened or if there was other evidence of clinical failure. The recurrence of the lesion in our patient was probably due to poor compliance with the antifungal agents he was administered, namely, KI, ketoconazole and itraconazole. Drug resistance was unlikely because there was a clinical response whenever he restarted regular treatment. In addition, the isolate was sensitive to ß uconazole by drug susceptibility testing. To conclude, we report a case of primary cutaneous aspergillosis due to *Aspergillus niger* in an immunocompetent host that recurred owing to irregular treatment.

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