CASE REPORT

# Co-infection of invasive pulmonary aspergillosis and cutaneous *Fusarium* infection in a patient with pyoderma gangrenosum

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We report an unusual case of co-infection of invasive pulmonary aspergillosis (IPA) and fusarial skin infection in a patient with classic pyoderma gangrenosum with unknown causes, which were previously controlled with oral prednisolone, cyclosporine. The diagnosis was made on direct microscopy and culture of endobronchial washing, bronchoalveolar lavage and skin lesion biopsy. The treatment failed, and the patient expired 12 days following hospitalization. This report highlights the rarity of coexistence of IPA and a chronic fusarial skin infection and thereby reinforcing the physician's attention toward the possibility of invasive fungal infection in the immunosuppressed patients.

**Key words:** *Aspergillus*, *Fusarium*, invasive pulmonary aspergillosis, pyoderma gangrenosum

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## INTRODUCTION

Invasive fungal infections (IFIs) have an increased frequency in the immunocompromised patients and are major causes of morbidity and mortality.[1] The incidence and mortality rates of IFI may vary considerably based on immune status and the management of the patients and the environmental infection control of the ward and hospitals.[2] Reported incidences and mortality rate of invasive aspergillosis extremely variable in different patient groups, affecting 24-60% of those with chronic granulomatous disease, acute leukemia and organ transplant recipients and patients with long-term steroid use or profound neutropenia.[3,4]

In report by *Aspergillus* study group the occurrence of IA in hematological patients reported more than 60%.[5] The mortality rate can exceed 90% in bone marrow transplant recipients.[6] It seems that mortality rate for aspergillosis has declined from 60-70% to approximately 40%.[2,7] As these fungi are ubiquitous in environment and always isolated from skin and respiratory secretion, The diagnosis needs to be confirmed using both culture and histopathology.[8] Pyoderma gangrenosum (PG) is a rare cutaneous disease and often appears as an inflammatory nodule or pustule with gradual peripheral enlargement.[9,10] Clinically it starts with sterile pustules rapidly progresses and turn into painful ulcers of variable depth and size with undetermined violaceous borders. Course could be mild or malignant, chronic or relapsing with marked morbidity. In many cases, PG is related to an underlying disease, most commonly with inflammatory bowel disease, collagen vascular, rheumatic or hematological diseases, viral infections and malignancy. Approximately, 25% of cases are not associated with any underlying disease. Diagnosis of PG is based on history of an underlying disease, typical clinical presentation, histopathology, and excluding the other diseases that could lead to similar appearance. The peak of incidence occurs between the ages of 20-50 years more often in women. Etiology has not been cleared yet.[11] The treatment of PG is often done by systemic corticosteroids or nonsteroidal immunosuppressive agents, such as, azathioprine and cyclosporine. Systemic corticosteroids or other T-cell suppressive agents have been considered to predispose patients to infection. We describe an acute ill-patient with progression

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of the chronic PG lesions, despite treatment, therefore, was subjected to further evaluation for the possibility of secondary infection.

## CASE REPORT

In 2012, a 32-year-old man with 5-year history of classic PG was admitted to the Intensive Care Unit of Shafa Hospital (Sari, Iran) with a complaint of cough, sputum and dyspnea in the last 4 days. The patient had received methylprednisolone pulses 1 week prior to admission. His current medication was oral prednisolone, cyclosporine and surgical wound therapy. The diagnosis of PG was confirmed by biopsy, but the cause was left unknown. On physical examination, the patient had respiratory rate of 30 breaths/min, temperature of 39°C, heart rate of 150 beats/min, oxygen saturation (below 90%). Large and deeply diffuse necrotic skin lesions appeared on the upper limbs and over the chest and back [Figure 1]. During dermatology examination, skin lesions were observed, and initial lung and heart examinations were unremarkable. Initial laboratory evaluation showed: White blood cell count was $9.8 \times 10^{9/1}$ with a differential of 79% neutrophils, 22% lymphocytes, 3% monocytes, and 1% eosinophil. Platelets were $25 \times 10^{9}$/L. No vegetation was found in transthoracic echocardiogram. A computed tomography (CT) scan of the lungs revealed multiple 1-2 cm nodules in various stages with feeding vessels sign and cavitations in some of them, well as the halo sign, an area of low attenuation surrounding a nodular lesion, and the air-crescent signs with small size left pleural effusion [Figures 2 and 3]. Respiratory failure developed 2 days after admission, and patient was intubated and mechanically ventilated. Bronchoscopy was performed, and bronchoalveolar lavage (BAL) specimen was obtained. The diagnosis of probable invasive pulmonary aspergillosis (IPA) was made on based on European Organization for Research and Treatment of Cancer/IFIs Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group definitions.[12] Direct microscopy examination of endobronchial washing and BAL samples demonstrated acute branching septate hyphae, consistent with aspergillosis and the culture of the samples revealed *Aspergillus flavus*. The diagnosis of cutaneous fusariosis was made on *Fusarium proliferatum* is isolated from skin lesion biopsy in multiple media. The polymerase chain reaction assays have been performed with BAL sample and tissue biopsy. The fungal internal transcribed spacer (ITS) region of rRNA gene in these samples were amplified and sequenced for accurate identification of the fungal species. The ITS sequences of *A. flavus* and *F. proliferatum* were submitted to the NCBI GenBank and received the accession no. KJ000075 and KJ000076, respectively. The voriconazole (6 mg/kg body weight IV. BD) and antimicrobial drugs such as linezolid (600 mg BD), meropenem (1 g IV. TDS), and ciprofloxacin (400 mg BD) were administered to treat fungal and bacterial infection. The dose of these drugs was adjusted based on creatinine

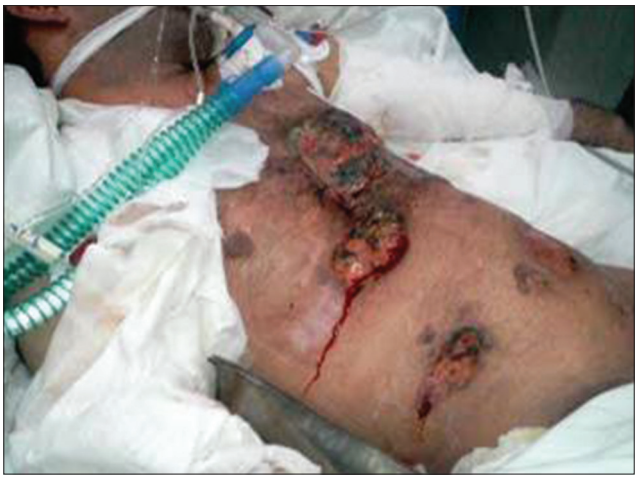

**Figure 1:** Large and diffuse deeply necrotic skin lesions were found on upper limbs and over the chest and back

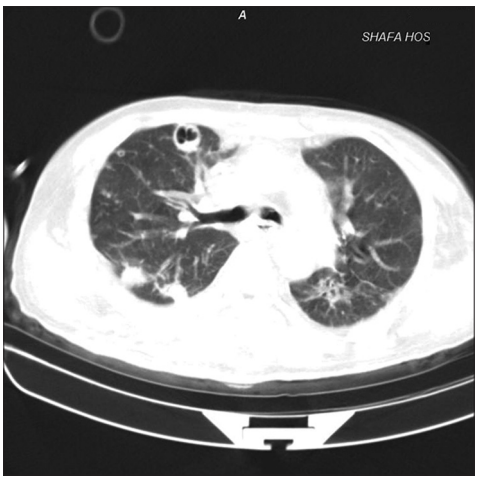


**Figure 2:** Computed tomography scan of the lungs reveal two nodules with irregular borders in the posterior segment of the right upper lobe. A cavity lesion is in the anterior segment of the right upper lobe

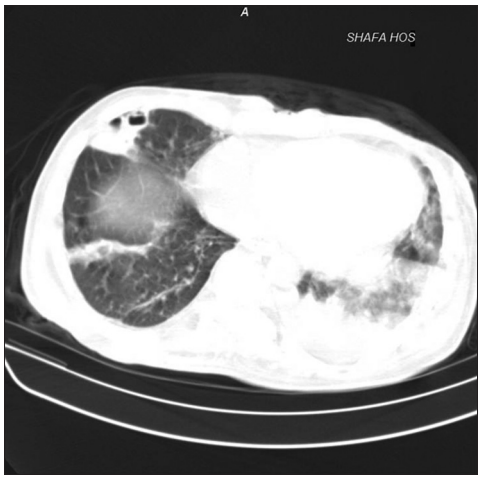


**Figure 3:** Computed tomography scan of the lungs showing two cavitary lesions in the right middle lobe. There is a patchy consolidation in the left lower lobe. Pleural effusion on the left side is also seen

clearance. The treatment failed, and the patient expired 12 days following hospitalization due to sepsis.

## DISCUSSION

Systemic corticosteroids have been considered to predispose patients to infection, but there is a little report on the invasive fungal infection.[8] *Aspergillus* and *Fusarium* species are saprophytic fungus with worldwide distribution. They can grow on most decaying organic materials. This fungus has recently emerged as the two most common pathogenic mold, which can cause disseminated invasive fungal disease in severely immunocompromised patients.[12-14] In our patient, using of long-term systemic corticosteroid and the multiple debridement could be a predisposing factor in developing of the invasive IPA and cutaneous *Fusarium* infection. Corticosteroids influence the function of neutrophils and lymphocytes and stimulate the growth of *Aspergillus*.[13] In the compromised host, *Aspergillus* colonizes the tracheobronchial tree, invades the walls of large bronchi, but less the trachea, leading to a focal or diffuse and intense acute inflammatory reaction along with ulceration and endoluminal sloughing of the epithelium, hyphae, mucus and cellular debris. When infection is limited to the airway canal or has minimal, patchy extension into the surrounding parenchyma, the chest images are normal or reveal foci of atelectasis, that is due to the local airway obstruction by hyphae laden mucus and inflammatory debris, but the patients might be quite symptomatic.[15]

The genus *Aspergillus* comprises about approximately 200 species.[8] *Aspergillus fumigatus* is the most common species isolated from invasive aspergillosis cases, followed by *A. flavus* and less commonly *Aspergillus niger* and *Aspergillus terreus*. *A. flavus* survives at higher temperatures and a predominant pathogen in areas with hot and dry climates.[16,17] *A. flavus* produces potent hepatotoxin known to man. The culture of the BAL specimens and the biopsy of the skin lesion afforded the microbiological and histopathological clues for diagnosis of invasive fungal infection. On the CT images, lesions of invasive aspergillosis may often show characteristic appearance. The most common appearance is a rounded mass, representing necrotic lung, infiltrated with *Aspergillus hyphae*,[9] surrounded and separated from normal lung by a thin zone of ground-glass opacity with lower attenuation than the surrounding normal lung.[18,19] This characteristic appearance termed the "CT halo sign. The halo of ground-glass attenuation pathologically represents pulmonary hemorrhage.[19] Though this sign is not specific for IPA but this sign is most often secondary to IPA. The halo sign appears early in the course of infection, often preceding the development of cavitations or air crescent by 2-3 weeks.[18]

Despite radiographic regressions of the infection, IPA does not frequently extend into the pleural space to form an empyema. Pleural aspergillosis is more frequently a complication of thoracic surgery or the result of rupture of a mycetoma cavity into the pleural space.[19,20]

In our case, CT halo sign which is highly specific for invasive aspergillosis was presented before getting the positive microbiological and histopathological results. The patient had a stable course of PG under maintenance therapy with oral prednisolone. Furthermore, 1 week prior to admission he had received methylprednisolone pulses due to the progression of lesions. Hospitalization and the skin biopsy did not favor the progression of PG.

Pyoderma gangrenosum is a rare, inflammatory, non-infective and nonneoplastic skin disorder, often associated with systemic diseases, such as inflammatory bowel disease, rheumatoid arthritis or hematological malignancy, but up to 50% of patients have some degree of variations. The cause of PG remains obscure, It is believed that it has no relation with bacterial infection, hence makes the term pyoderma redundant.[21]

*Fusarium* species are filamentous saprophyte with worldwide distribution in the soil and air. They cause superficial, locally invasive, and disseminated infections in humans. The clinical form of fusariosis depends largely on the immune status of the host and the portal of entry. Invasive and necrotic fusarial skin infections are rare and found in immunosupressed subjects.[14,22] *Fusarium* species have recently appeared as the second most prevalent pathogenic mold in immunocompromised patients and are moderately resistant to most antifungals. The fusarial skin infection typically manifests as multiple red or violaceous macules or nodules, often ulcerated and covered by a black eschar.[23] We speculate that the skin lesions of our patient was localized and as a result of skin breakdown caused by multiple surgical debridement and corticosteroid pulse therapy. These lesions are erythematous, papular or nodular, painful, and frequently with central necrosis giving the lesions an echthyma gangrenosum like appearance. Fusarial skin lesions can involve any site, with a predominance in the extremities, and evolve rapidly, usually within few days.[24]

Patients with IFIs are now classified according EORTC/MSG consensus group definitions.[12] These definitions may serve as a useful model for improving the quality of clinical studies and diagnosis with a variable certainty including proven, probable or possible groups. Diagnosis of probable IFI in our patient was based on host factor, clinical criteria and mycological finding. The host factor of our patient was prolonged use of corticosteroids. The two signs of lower respiratory tract involvement including a halo and air-crescent revealed in CT. Direct microscopy exam and

the fungi grown in culture media constituted mycological support. In this case study, autopsy and biopsy were not performed; therefore, we were not able to report the definite IPA and fusarial infection.

Voriconazole is often used for the treatment of serious infections caused by *Aspergillus* and *Fusarium*. Baden *et al*., demonstrated that in severely immunocompromised patients with life-threatening IFI who have failed or intolerant to standard antifungal therapy, voriconazole had a substantial efficacy, but with an acceptable level of toxicity.[25]

The study subject had progressive respiratory failure and ulcerative lesions and unresponsive to prompt voriconazole therapy. Alternative options to traditional amphotericin B treatment could be considered if clinical response is not satisfactory. The alternative includes high-dose liposomal amphotericin B that has the highest effect against *Aspergillus* and *Fusarium* species, whereas itraconazole had no activity against *Fusarium* species. It was found that caspofungin efficacy during empirical antifungal therapy in neutropenic patients or severely ill-patients with refractory invasive *Aspergillus* infections but administration of anidulafungin is generally avoided due to the intrinsic resistance.[26-28]

The present report highlights the rarity of coexistence of Invasive IPA and cutaneous *Fusarium* infection in a patient with chronic PG, and should bring the attention of physicians toward the possibility of invasive fungal infection superimposed on chronic skin lesion. Early skin biopsy and CT scan are recommended for the early diagnosis.

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## AUTHOR'S CONTRIBUTION

TS contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. NA contributed in the conception of the work, drafting, approval of the final version of the manuscript, and agreed for all aspects of the work. MA contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. SM contributed in the conception of the work, approval of the final version of the manuscript, and agreed for all aspects of the work. NN contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. RA contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. ON contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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