www.jmscr.igmpublication.org *Impact Factor 1.1147*

ISSN (e)-2347-176x

IGM Publication Journal Of Medical Science And Clinical Research An Official Publication Of IGM Publication

Fulminant Invasive Pulmonary Aspergillosis In Immunocompetent Patients

A Report of two Cases

Authors

Ghosh (Ray) Reena[1], Banerjee Debarati[2], Sugata Dasgupta[3] Rathindranath Ray[4], Prof. Tamal Kanti Ghosh[5]

[1, 2] Department of Microbiology, R.G.Kar Medical College & Hospital.
[3]Department of Anaesthesiology & Critical Care, R.G.Kar Medical College & Hospital
[4]Department of Gynae & Obs. Calcutta National Medical College & Hospital
[5]Professor Department of Pathology & Principal, Midnapore Medical College,Midnapore

Corresponding Author
Ghosh (Ray) Reena
Email: *ghoshreena@hotmail.com*

Abstract:
Two cases of invasive aspergillosis (IA) in immunocompetent patients with a fulminant fatal outcome are reported. Both patients had a history of chronic lung disease treated with prolonged corticosteroid inhalation and a short course of systemic corticosteroids. They presented with dyspnea and fever, their respiratory function deteriorated rapidly and they succumbed to the disease. Aspergillus fumigatus was cultured from deep tracheal aspirate (DTA) samples of both patients. In the first case, IA diagnosis was confirmed by thoracic CT scan along with isolation of Aspergillus fumigates in blood culture. These two cases demonstrate that short term systemic corticosteroid therapy in immunocompetent patients with underlying chronic lung condition is a risk factor for IA. Invasive aspergilosis should be suspected in COPD patients receiving steroid treatment who have extensive pulmonary infiltrates in initial chest X-ray. More judicious use of corticosteroids may help prevent occurrances of IPA (invasive pulmonary aspergillosis) with its attendant serious morbidity and high mortality.
Key-words:Invasive aspergillosis(IA), Aspergillus fumigates, corticosteroids, immunocompetent patients, COPD.

INTRODUCTION

During the past decade, *Aspergillus* spp. have become the most prevalent airborne fungal pathogens in developed countries, with a significant increase in invasive aspergillosis being observed[1]. *Aspergillus* is a saprophytic filamentous ubiquitous fungus. Of more than 350 species that belong to the genus *Aspergillus*, only *Aspergillus fumigatus* and *A. niger* produce disease in humans with any frequency. Although *Aspergillus* can affect any organ system, the respiratory tract is involved in more than 90% of affected patients. Humans have a remarkable capacity to eliminate aspergillus with the help of alveolar macrophages which phagocytose and destroy the inhaled spores. Nevertheless inhalation of *Aspergillus* spores or conidia can give rise to various clinical conditions, depending essentially on the host's immunological status[2]. In immunocompetent patients, pulmonary aspergilloma, allergic bronchopulmonary aspergillosis and obstructive bronchial aspergillosis are described. In immunocompromised patients, *Aspergillus fumigatus* can invade the pulmonary parenchyma, resulting in invasive pulmonary aspergillosis (IPA) which is an increasingly common cause of mortality and morbidity[3]. IPA is a life threatening fungal infection in immunocompromised patients particularly those with advanced stage of HIV infection, prolonged neutropenia or organ transplantation. Other predisposing factors, such as prolonged systemic corticosteroid therapy, solid malignancy, burns, chronic granulomatous disease and alcoholism, have been recognized[4]. In contrast, IA occurs very infrequently in immunocompetent patients. The isolation of Aspergillus from respiratory secretions of normal hosts usually signifies tracheobronchial colonization, not disease[5]. We report on two patients with a history of Chronic Obstructive Pulmonary disease (COPD with otherwise no immunodeficiency who developed invasive pulmonary aspergillosis with rapid fatal outcome after prolonged treatment with inhaled corticosteroid therapy and a short course of systemic corticosteroid therapy.

Case - 1:

A 68 yr old male patient, a chronic smoker who presented to the casualty with history of fever for 7 days before admission, severe cough, along with progressively increasing severe respiratory distress, chest pain and altered sensorium. He had a history of COPD for the last 10 yrs and on regular low dose inhalational corticosteroid along with inhaled bronchodilator since 1yr. He had no history of any heart disease, any solid organ transplantation or history of taking chemotherapy or any immunosuppressive drugs. One week before admission he had LRTI for which he was started on antibiotics (amoxycillin-clavulanic acid) and systemic (oral) corticosteroids (methylprednisolone) due to her worsening respiratory condition. On admission arterial blood gas (ABG) analysis showed Type2 respiratory failure with a PCO_2 of 115 mm of Hg .The patient was soon ventilated and started on antibiotics- Piperacillin-tazobactum and

Levofloxacin and put on intravenous corticosteroids. Bronchial aspirate and blood were sent for microbiological processing on day1. Blood for routine examination revealed increase in total leucocyte count (TLC) - 14000/c.mm (Neutrophil count >80%).Viral profile was normal. Chest X ray on day 1 showed bilateral diffuse patchy areas of infiltrates which worsened further on day 3 & day 5. Thoracic CT scan showed features of bronchiectatic and bronchiolectatic changes with peribronchial organizing and nodular infiltrates suggestive of pulmonary aspergillosis.

Case - 2:

A 45 yr old male patient, who was a known smoker, alcoholic and drug abuser. He had a medical history of COPD for the last 4 years with history of intermittent use of inhalational steroids along with regular inhalational bronchodilators. One month before admission, he had an acute exacerbation of COPD for which was treated with systemic corticosteroids (prednisone, 40 mg/day) in a gradually tapering dose for 7 days and levofloxacin for 5 days. He presented to the Emergency with a 48-hour history of fever, increasing dyspnea and wheezing. On admission, he had fever (101.4 °F), tachycardia (HR 130/min), tachypnea (38/min) and decreased oxygen saturation (80% - measured without oxygen). Auscultation showed bilateral diffuse rales with basal crepitations. Arterial Blood Gas analysis showed both Type1 & Type 2 respiratory failure (PaO_2=64mm of Hg; $PaCO_2$=88 mm of Hg). Routine blood picture showed leukocytosis (16,700/c.mm) with predominance of neutrophils and altered liver function test. Routine viral screening was negative. The patient was initially put on non invasive positive pressure ventilation but had to be ventilated the day after due to worsening of dyspnoea and Arterial Blood Gas analysis picture (Pa O_2=60 mm of Hg; $PaCO_2$=98 mm of Hg).He was started on Meropenem and Linezolid since admission. The patient did not respond to initial therapy with high dose of both inhaled bronchodilators and corticosteroids, and he had to be started on intravenous corticosteroids. An initial chest radiograph showed bilateral interstitial infiltrates with right lower lobe consolidation. Bronchial aspirate and blood culture samples were sent for microbiological examination. The bronchial aspirate was mucopurulent.

MICROBIOLOGICAL WORK UP

Gram stained smear of bronchial aspirate of the first patient showed few Gram positive hyphae with plenty of pus cells and few Gram positive cocci in clusters and chains. However bronchial aspirate of second patient showed plenty of Gram positive hyphae and few Gram negative bacilli. 20%KOH mount showed hyaline septate fungal hyphae with dichotomous branching. Culture on MacConkey agar and chocolate agar showed no growth but on blood agar white cottony colonies were seen after 24 hours incubation at 37ºC which showed Gram positive hyphae. Simultaneously fungal culture of the respiratory samples of both patients was done on Sabouraud's dextrose Chloramphenicol agar.

Primary isolations in SDCA at 37ºC and 25ºC showed appearance of velvety smoky green colonies after 72 hours incubation, the reverse of which was tan to pale brown in colour. Lactophenol cotton blue mount from these colonies showed short and smooth conidiophores with flask shaped vesicle, uniseriate phialides usually covering upper half of vesicle parallel to the axis of the stalk, bearing echinulate nearly globose conidia in chains. Based on the above macroscopic and microscopic findings the fungus was identified as *Aspergillus fumigatus.* Repeat bronchial aspirate samples on day 3 from both patients also showed growth of *A.fumigatus.* Blood culture of 1st patient showed scum formation on day 3 of aerobic incubation at 37ºC, subculture from which was done on routine media as well as on SDA & SDCA. Culture on MacConkey agar, blood agar and chocolate agar showed no growth, while culture on SDA and SDCA showed colonies suggestive of *A.fumigatus.* Blood culture from the 2nd patient however showed no growth after 7 days of aerobic incubation at 37ºC.

In vitro Semisolid Agar Antifungal Susceptibility (SAAS) testing method performed as suggested by Khan S *et al* [6] in 2006 for a resource constrained laboratory. MIC was determined using known increasing concentrations of fluconazole & voriconazole in BHIB with 0.5% agar by Agar Dilution method comparing with drug free control. The MIC range of fluconazole was kept between 2-64 µgm/ml while the MIC range of voriconazole was 0.125-2 µgm/ml. *A.fumigatus* ATCC was resistant to Fluconazole at all concentrations and sensitive to voriconazole with an MIC-0.25 µgm/ml. MIC of voriconazole for the 2 fungal isolates from the two patients found to be 0.5 & 1 µgm/ml respectively which denotes both the isolates were sensitive to voriconazole. Both the patients were started voriconazole.The first patient responded but was discontinued from therapy due to financial constraints and he succumbed to the disease.The 2nd patient however developed multiorgan failure and died after receiving only 2 doses of the drug. Limitations of this study were that lung biopsy and autopsy could not be performed for both the patients.

DISCUSSION

Both of these patients presented with rapidly progressive pulmonary IA despite no clinical history of documented immunodeficiency. These cases highlight that invasive pulmonary aspergillosis can occur in immunocompetent individuals with COPD even in the absence of risk factors such as corticosteroid or cytotoxic therapy, use of broad- spectrum antimicrobial agents, severe granulocytopenia or qualitative granulocyte defects. Both patients had chronic bronchial disease, for which they received long-term low doses of inhaled corticosteroids and a short course of systemic corticosteroids a few days before admission, which have rarely been reported to be a risk factor for fulminant IA in otherwise immunocompetent patients. The increased risk of IA in patients with prolonged corticosteroid therapy has long been documented. The precise dose and duration of corticosteroids that significantly increase the risk of IA have not yet

been well defined. Some authors have noticed that, in most IA patients treated with steroids, the duration of steroid therapy prior to aspergillosis has been longer than 3 weeks[7]. However Palmer et al[8] reported that the threshold steroid level varies according to the type of patients and emphasized that in the setting of underlying lung disease there is a risk of IPA at much lower dosages. Rello *et al*.[9] in their study have also reinforced that steroid use, even at low dosages, is an important factor in the development of IPA in patients with COPD who are exposed to or previously colonized with *Aspergillus* species. Our two cases also depict that in patients with chronic lung disease the risk of IA is likely to occur at much lower doses or with much shorter durations of corticosteroid therapy. The inhaled corticosteroids could also have played a role in our patients, since rare IA cases have been associated with inhaled corticosteroid therapy[10,11].The dramatic rapidity of the fungal dissemination from the primary pulmonary infection was evident from the fact that both patients had fungal septicaemia and both the patients died 7-8 days after admission from multiorgan dysfunction. Rello *et al*[8] have described similar rapid progression in eight patients with chronic obstructive pulmonary disease (COPD).Brown E *et al*[12] also reported about an adult patient without such a predisposition, who had a rapidly progressive respiratory failure with a fatal outcome associated with repeated growth of *Aspergillus fumigatus* on culture of sputum and bronchoscopy specimens.

The diagnosis of invasive pulmonary aspergillosis is often difficult. This diagnostic possibility should be considered when an aetiological agent is not identifiable in a patient, who fails to respond to antimicrobial agents. Sputum cultures may be negative. Positive cultures have to be interpreted taking into consideration the fact that the organism colonizes the upper and lower respiratory tract without causing manifestations of the disease. Histological evidence requires invasive methods to obtain diagnostic samples, and both clinicians and patients may be reluctant for undertaking these invasive techniques. Common diagnostic procedures include CT scan and bronchoscopy or bronchoalveolar lavage with washings, which is safe and sensitive and particularly useful in high-risk patients where organisms may be identified quickly with smear[13]

Although invasive aspergillosis is often a fatal disease, some studies have shown that early diagnosis and institution of appropriate treatment, together with reduction in risk factors, appears to significantly improve the prognosis[13]. Raja et al described a 34-year-old immunocompetent male patient in whom successful treatment of this infection was achieved with amphotericin B and itraconazole [14]. Even Ali *et al*[14] reported a case of IPA in a known COPD otherwise immunocompetent male who got completely cured with Amphotericin B therapy.

These two cases demonstrate that short-term systemic corticosteroid therapy and prolonged

inhalational corticosteroid even in immunocompetent patients with underlying chronic lung conditions may be a risk factor for IA and, furthermore, for its rapid evolution and fatal outcome. There are increasing reports describing IPA in patients with COPD without the classic risk factors for this severe infection. The majority of these patients have advanced COPD and/or on corticosteroid therapy with nonspecific clinical and radiological presentation.The 100% mortality observed for these 2 cases emphasises that every effort should be made to obtain an early diagnosis for prompt institution of antifungals in order to improve the chance of survival in these patients.

Figures :

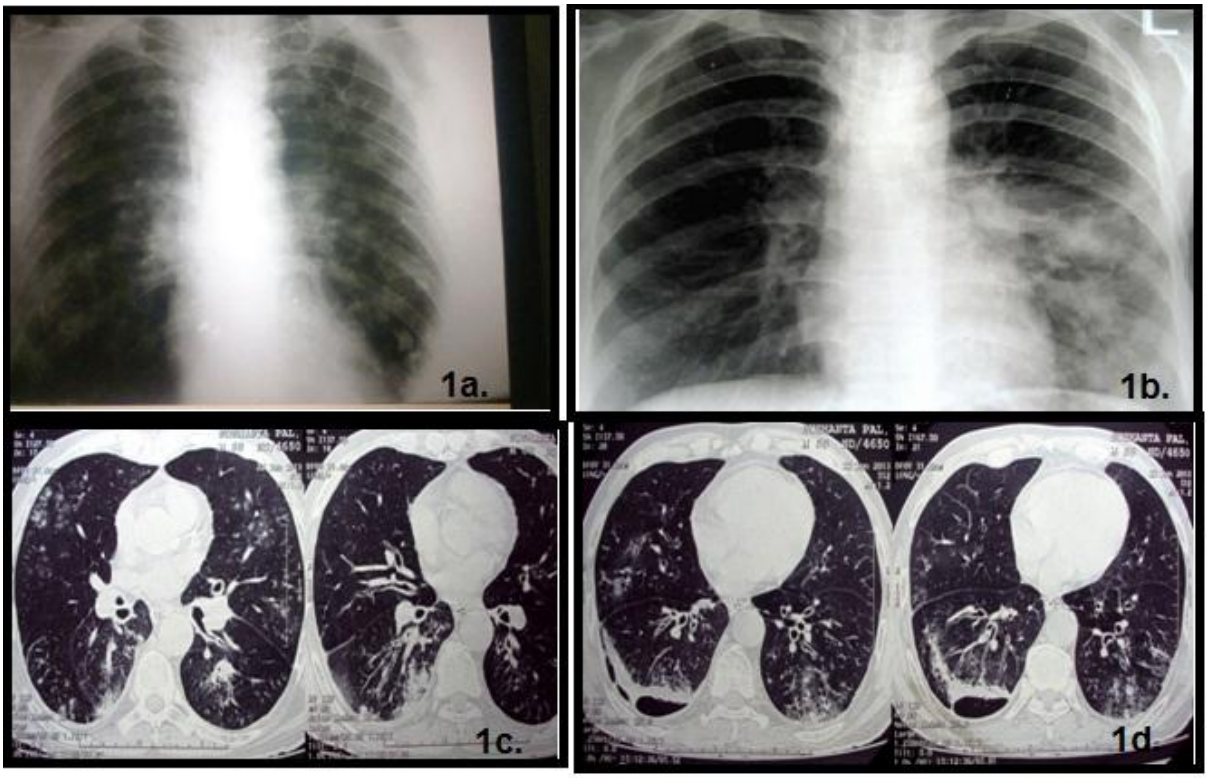

Image 1.

1a. X Ray of 1st patient showing bilateral diffuse patchy areas of infiltrates.

1.b. X-RAY of 2nd patient showed bilateral interstitial infiltrates with right lower lobe consolidation

1.c.CT scan pictures of 1st patient showing bronchiolectatic changes with peribronchial organizing .

1.d.CT scan pictures of 2ndpatient showing bronchiolectatic changes with focal. nodular infiltrates,

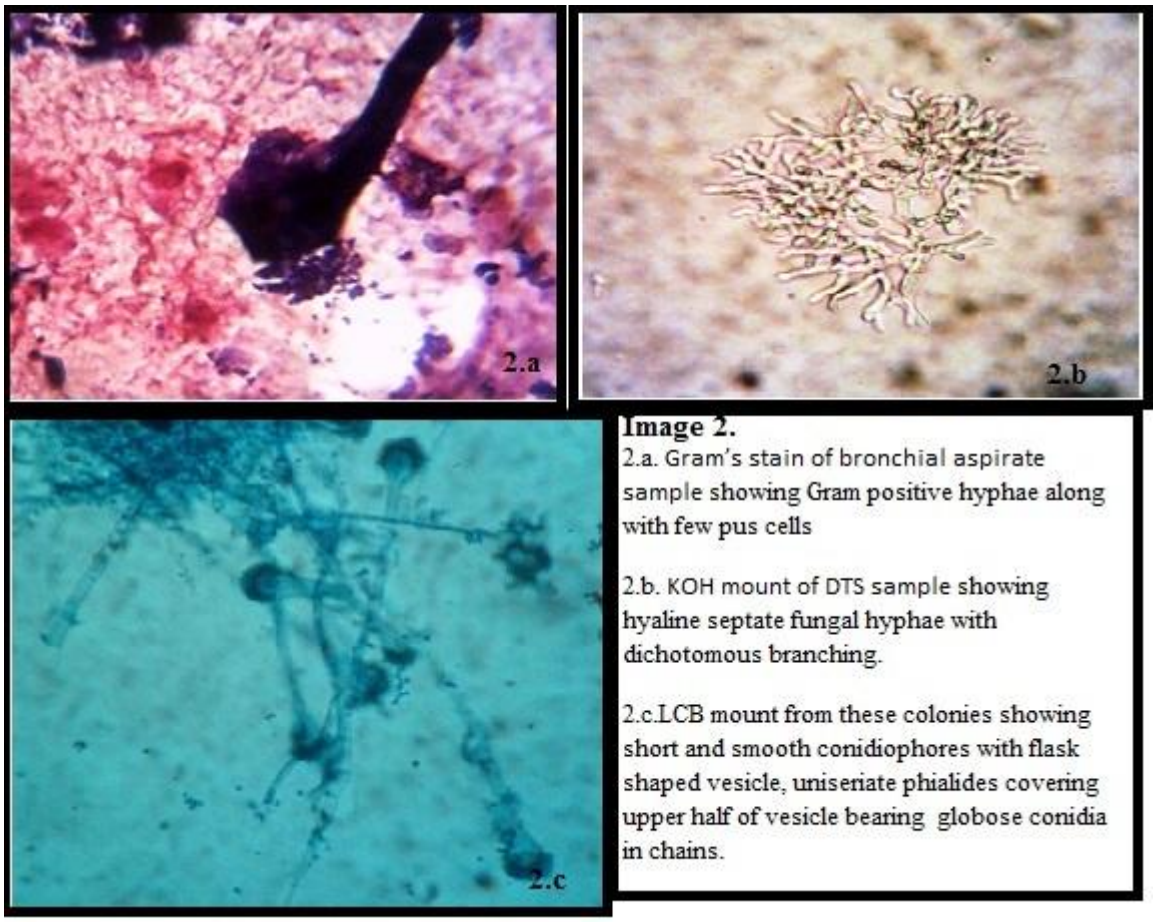

Image 2.

2.a. Gram's stain of bronchial aspirate sample showing Gram positive hyphae along with few pus cells

2.b. KOH mount of DTS sample showing hyaline septate fungal hyphae with dichotomous branching.

2.c.LCB mount from these colonies showing short and smooth conidiophores with flask shaped vesicle, uniseriate phialides covering upper half of vesicle bearing globose conidia in chains.

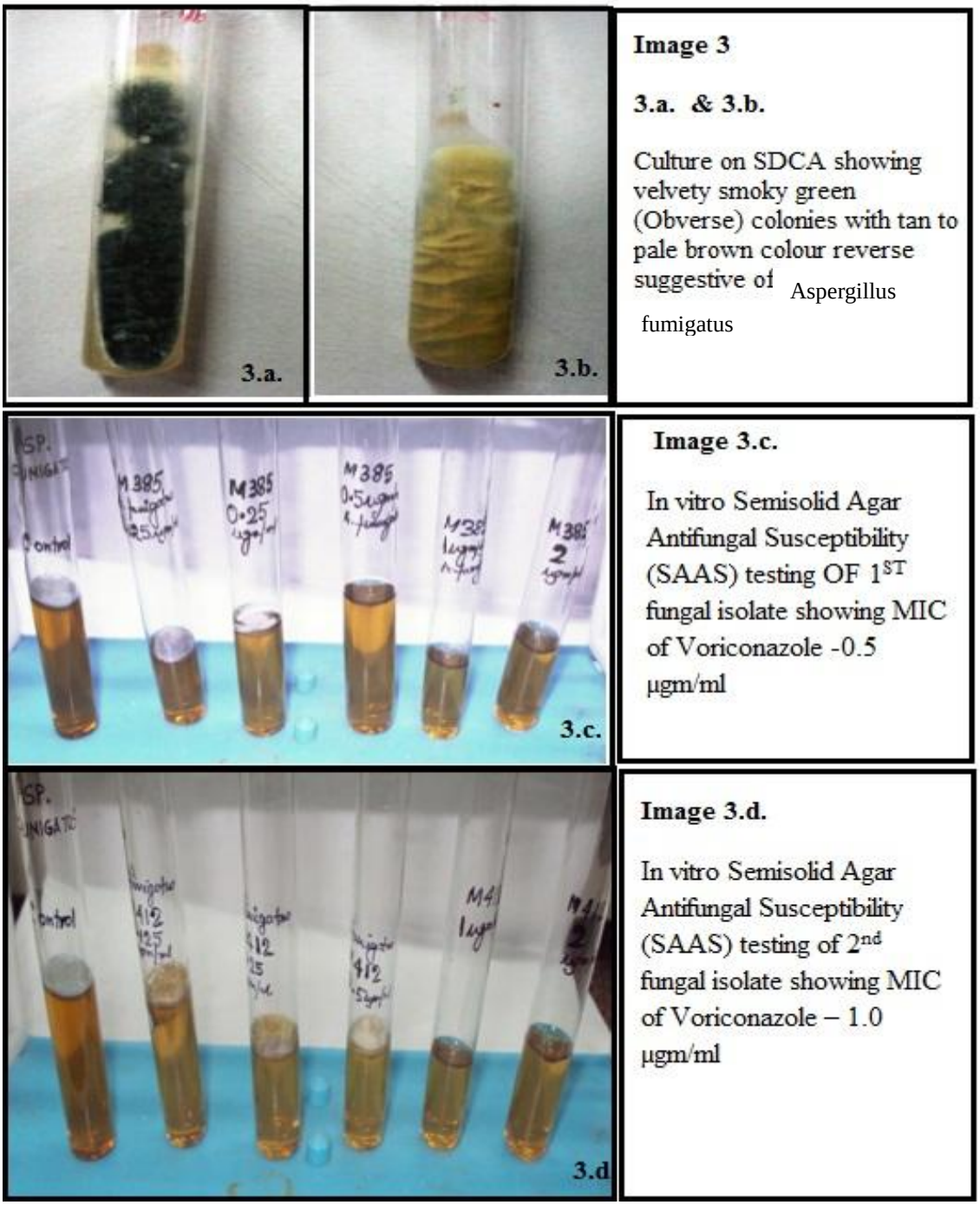
3.a.
3.b.
Image 3
3.a. & 3.b.
Culture on SDCA showing velvety smoky green (Obverse) colonies with tan to pale brown colour reverse suggestive of Aspergillus fumigatus
3.c.
Image 3.c.
In vitro Semisolid Agar Antifungal Susceptibility (SAAS) testing OF 1ST fungal isolate showing MIC of Voriconazole -0.5 µgm/ml
3.d
Image 3.d.
In vitro Semisolid Agar Antifungal Susceptibility (SAAS) testing of 2nd fungal isolate showing MIC of Voriconazole – 1.0 µgm/ml

Figure 1

REFERENCES:

1) Steinbach WJ, Stevens DA, Denning DW, Moss RB. Advances against aspergillosis. Clin Infect Dis 2003; 37(suppl 3):155–56.
2) Sharma OP, Chwogule R: Many faces of pulmonary aspergillosis. Eur Respir J 1998; 12:705-15.
3) Vandewoude KH, Blot SI, Depuydt P, Benoit D, Temmerman W, Colardyn F. Clinical relevance of Aspergillus isolation from respiratory tract samples in critically ill patients. Critical Care 2006; 10(1):R31.
4) Cornet, M., Mallat, H., Somme, D., Guérot, E., Kac, G., Mainardi, J. L., Fornes, P., Gutmann, L. and Lavarde, V. Fulminant invasive pulmonary aspergillosis in immunocompetent patients—a two-case report. Clinical Microbiology and Infection 2003; 9(12):1224–27.
5) Karam GH, Griffin FM Jr. Invasive pulmonary aspergillosis in non-immunocompromised, non-neutropenic hosts. Rev Infect Dis1986; 8: 357–63.
6) Khan.S, Singhal.S, Mathur.T, Upadhay.DJ, Rattan.A . Antifungal susceptibility Testing method for resource constrained laboratories. Indian J of Med Microbiol 2006; 24(3): 171-76.
7) Rodenhuis S, Beaumont F, Kauffman HF, Sluiter HJ. Invasive pulmonary aspergillosis in a non-immunocompromised patient: successful management with systemic amphotericin and flucytosine and inhaled amphotericin. Thorax 1984; 39: 78–79.
8) Palmer LB, Greenberg HE, Schiff MJ. Corticosteroid treatment as a risk factor for invasive aspergillosis in patients with lung disease. Thorax 1991;46:15–20.
9) Rello J, Esandi ME, Mariscal D, Gallego M, Domingo C, Valles J. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: report of eight cases and review. Clin Infect Dis 1998; 26:1473–75.
10) Ortuño F, Cabello NJ, Salaverria I, Vazquez S. Probable invasive pulmonary aspergillosis and inhaled steroids treatment. Enferm Infecc Microbiol Clin 2002; 20: 131–32.
11) Leav BA, Fanburg B, Hadley S. Invasive pulmonary aspergillosis associated with high-dose inhaled fluticasone. N Engl J Med2000; 343: 586.
12) Brown E, Freedman S, Arbeit R, Come S. Invasive pulmonary aspergillosis in an apparently non-immunocompromised host. Am J Med.1980; 69(4):624-27.
13) Ali Z A, Ali A A, Tempest M E, Wiselka M J. Invasive pulmonary aspergillosis complicating chronic obstructive pulmonary disease in an immunocompetent patient. J Postgrad Med 2003;49:78-80.
14) Raja NS, Singh NN. Disseminated invasive aspergillosis in an apparently immunocompetent host. J Microbiol Immunol Infect. 2006; 39(1):73-77.