Original Article

Invasive pulmonary aspergillosis in oncological setting with use of newer vascular endothelial growth factor receptor inhibitor

Javvid Muzamil, Faisal R. Guru, Ansar Hakim, Firdousa Nabi[1]

Department of Medical Oncology, Sher-I-Kashmir Institute of Medical Sciences, [1]Department of Prosthodonsia, Government Dental College, Srinagar, Jammu and Kashmir, India

ABSTRACT

Background: Invasive pulmonary aspergillosis is a major cause of morbidity and mortality in neutropenic patients. Microbiological and serological tests are of limited value. The diagnosis should be considered in neutropenic patients with fever not responding to antibiotics, and typical findings on thoracic computed tomography scan. Whenever possible, diagnosis should be confirmed by tissue examination. Newer serological techniques like β-D-Glucan Assay and Galactomannan assay are used in diagnosis and monitoring therapy in such patients. **Aim:** To early diagnose Invasive pulmonary aspergillosis and to decrease mortality. **Methods:** A total of 150 patients of hemato-oncological malignancies were prospectively enrolled intostudy. **Results:** Only 10 (6.6 %) patients developed invasive pulmonary aspergillosis and mortality was 30%.Patients were treated medically with never azoles and echinocandin antifungals, with long term survival in seven patients and early mortality in rest of patients. **Conclusion:** IPA is a difficult infection to treat in immucompromised state. It needs very high degree of suspicion to diagnose. Sick patients should be treated with combination antifungal of different mechanisms at outset and therapy should be continued for six months.

Key words: Autologous stem cell transplant, high-resolution computed tomography, human immunodeficiency virus, invasive pulmonary aspergillosis, vascular endothelial growth factor receptor

INTRODUCTION

Pulmonary aspergillosis refers to a spectrum of diseases that result from aspergillus becoming resident in the lung. These include invasive aspergillosis from angioinvasive disease, simple aspergilloma from inert colonization of pulmonary cavities, and chronic cavitary pulmonary aspergillosis from fungal germination and immune activation. Aspergillus fumigatus is by far the most common pathogenic species in humans where the small size and hydrophobicity of its spores confer a dispersion advantage.[1-3]

Invasive aspergillosis has been described classically in neutropenic patients in the setting of hematologic

Address for correspondence:
Dr. Javvid Muzamil, Married Hostel Room Number F16, Department of Medical Oncology, Sher-I-Kashmir Institute of Medical Sciences, Soura, Srinagar - 190 011, Jammu and Kashmir, India.
E-mail: javvidmd@gmail.com

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malignancy but is seen increasingly in patients with even milder immune compromise from immunosuppression, chronic pulmonary or liver disease, or critical illness.[4] As the portal of entry, the upper and lower respiratory tracts are most commonly infected although dissemination to any organ may occur. Aspergillus tracheobronchitis and central nervous system infection are associated with especially poor outcomes. Early diagnosis of invasive aspergillosis, along with the use of therapeutic agents with greater tolerability and efficacy, has the potential to decrease mortality, which remains high.

Criteria for the diagnosis of invasive fungal disease were formulated in 2002 and updated in 2008.[5] Proven invasive aspergillosis requires histopathologic or cytologic evidence of fungus, or culturing aspergillus from a sterile site regardless of immune status. The criteria for probable disease include clinical upper or lower respiratory tract involvement with direct (identification of fungus by microscopy, cytology, or culture) or indirect (detection of antigen or cell wall constituents) mycologic evidence of infection in a predisposed patient. The criteria for possible invasive aspergillosis are similar but mycologic evidence is not required.

Populations predisposed to invasive aspergillosis are:

- Allogeneic stem cell transplant
- Neutropenia for >10 days
- Anti-T-cell agents, calcineurin and tumor necrosis factor inhibitors, purine analogs
- Systemic corticosteroid used for 3 weeks
- Inherited severe immunodeficiencies
- Solid organ transplant
- Critical illness
- Chronic liver disease
- Chronic obstructive pulmonary disease (COPD)
- Diabetes mellitus
- Human immunodeficiency virus (HIV) infection.

The clinical presentation of invasive pulmonary aspergillosis (IPA) includes fever, cough, dyspnea, chest discomfort, and hemoptysis. Chest computed tomography (CT) imaging is more sensitive than plain chest radiography. Chronic liver disease and COPD signs on CT scans constituting clinical evidence for invasive pulmonary disease by the 2008 criteria include dense, well-circumscribed lesion(s) with or without a surrounding "halo" of ground-glass gray attenuation, air crescent sign, and cavity formation. Tests that may aid in the diagnosis of invasive infection include an enzyme immunoassay that detects galactomannan antigen, a constituent of the aspergillus cell wall, and quantitative polymerase chain reaction (PCR) assay. The sensitivity and specificity of these tests vary depending on the host (immunocompromised *vs.* nonimmunocompromised), the specimen tested (serum or bronchoalveolar lavage [BAL] fluid), and the presence of antifungal therapy, which can decrease assay sensitivity.[6-8] There may be a role for serial tests both in screening high-risk patients and in assessing response to therapy.

Guidelines favor voriconazole as the initial treatment of IPA based on its greater activity *in vitro* and a randomized trial showing improved outcomes and a lower rate of adverse reactions compared with amphotericin B.[9-10] Voriconazole is started intravenous (IV), then switched to oral therapy when clinical improvement occurs.

Medical therapy is often prolonged, with duration dependent on response, which includes assessment of clinical and radiographic resolution, microbiologic clearance, and improvement in immune function. Therapy may need to be restarted if immunosuppression, chemotherapy, or stem cell transplant is required. Several studies suggest that survival (64% at 12 weeks in one prospective study) may be higher than in the past.[11] In a retrospective cohort study of patents in the Intensive Care Unit without traditional risk factors for invasive aspergillosis, a delay in initiating antifungal therapy was associated with a longer hospital stay.[12]

Objectives and aims

- To see prevalence of IPA in hemato-oncological setting in indoor patients at our Tertiary Care Centre
- To see their outcome with treatment.

METHODS

A case study was carried out prospectively in our department over a period of 1 year on hemato-oncological malignancy patients who were in different phases of treatment. An informed consent was taken from all patients or guardians in case of minors. A total of 150 admitted patients for different protocols of chemotherapy were considered for the study. All patients enrolled in the study were HIV, hepatitis B and C negative. All patients underwent high-resolution CT (HRCT) chest at beginning and then symptomatic for chest complaints. Diagnosis of IPA was confirmed by HRCT finding and serological fungal assays. Finally, patients were treated for IPA with voriconazole and caspofungin. At the end, prevalence and survival were noted down.

RESULTS AND OBSERVATIONS

In total of 150 admitted patients for different protocols of chemotherapy, only 10 (6.6%.) patients developed IPA. Among the patients who developed aspergillosis, the median age was 31.5 years, with lowest age of 8 years and highest age of 60 years. Males were 70% (7), females were 30% (3) with male:female ratio of 7:3. Fifty percent (5) of patients were leukemic, 20% (2) were multiple myeloma, 20% (2) were

metastatic renal cell carcinoma, and 10% (1) were carcinoma breast.

Among metastatic renal cell carcinoma patients, both had metastasis to bones especially vertebral and rib metastasis. There was no nonskeletal metastasis. Average age was 57.5 years; both were males and former smokers. One patient was on 600 mg of pazopanib and other was on 800 mg of pazopanib and zoledronate. The average duration of treatment was 2.5 months. Both patients presented with nonproductive irritating nocturnal cough for average of 2 weeks and fever of 1-week duration. Both patients were very sick with SpO_2 of 85%. Patients were evaluated as an in-patient, with average hemoglobin of 11.0 g/dL, total leukocyte count of 3500 cells/μL, neutrophil count of 2000 cells/μL, platelet μL count of 70,000/μL, and erythrocyte sedimentation rate (ESR) of 55 mm/first hour. Blood and urine cultures were sterile. Arterial blood gas (ABG) revealed PO_2 of 55 mmHg, PCO_2 of 35 mmHg. Chest X-ray (CXR) revealed bilateral infiltrates with pneumatocele-like opacities [Figure 1]. Both patients were started on antistaph antibiotics, aminoglycosides and 4th generation cephalosporins and oxygen inhalation. This treatment was given for 2 weeks, but both patients persisted with symptoms. HRCT chest revealed characteristic halo and crescent signs of invasive aspergillosis [Figures 2-4]. Both patients had multiple pulmonary lesions of invasive aspergillosis. Blood was sent for galactomannan test and an average value of 0.5 was taken as cut off, with maximum value of 1.5. On β-D-glucan assay, average value was 80 mp/mL with maximum of 280 pg/mL. Rest of investigations such as kidney function test (KFT), liver function test (LFT), uric acid, and serum calcium were normal. Sputum for microscopic examination and culture came normal. Alkaline phosphatase was elevated to 250 IU (normal 70–150). Finally, IPA was established and patients were put on combination of injection caspofungin 50 mg once a day for 2 weeks and injection voriconazole 6 mg/kg two doses 12 h apart followed by 4 mg/kg twice daily for 4 weeks followed by oral

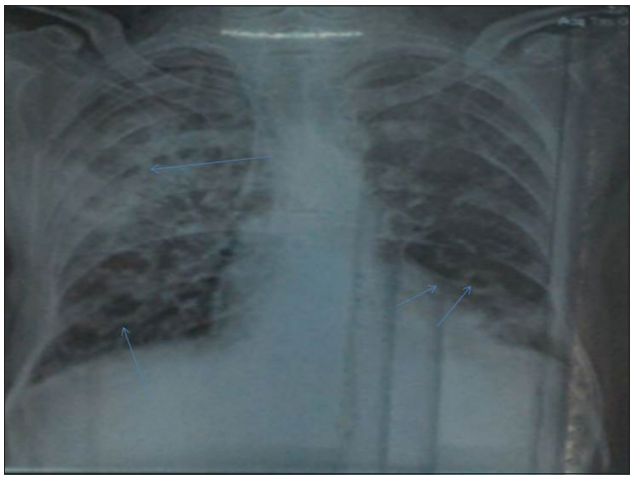

Figure 1: Chest X-ray revealed bilateral infiltrates with pneumatocele-like opacities

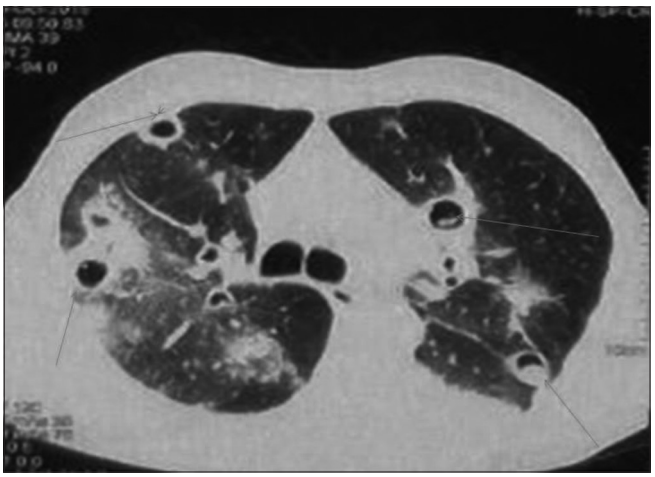

Figure 2: High-resolution computed tomography chest showing multiple aspergillus lesions in both lungs

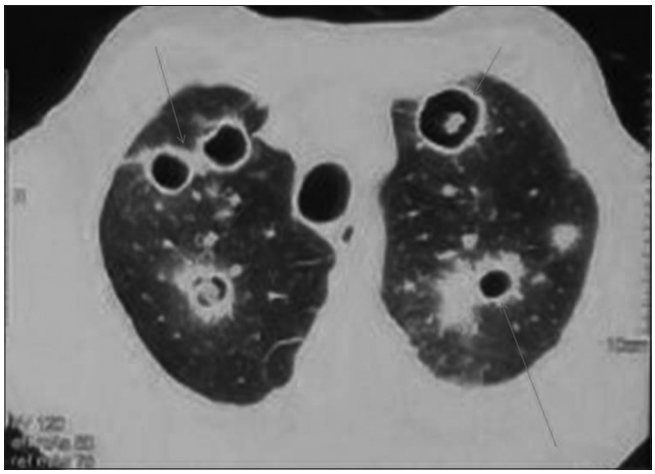

Figure 3: High-resolution computed tomography chest showing characteristic halo sign of invasive aspergillosis

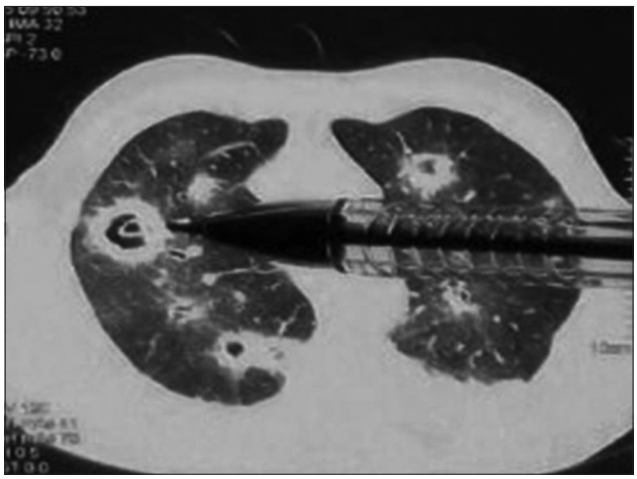

Figure 4: High-resolution computed tomography chest showing characteristic crescent sign of late phase of invasive aspergillosis

treatment for 6 months. Complete recovery was documented by repeating HRCT after 3 and 6 months of treatment. At 3 months, there was partial clearance and at 6 months, there was complete clearance. Treatment was continued for two more months as pazopanib was restarted after 1 month of start of antifungal therapy. Both patients are still continuing on vascular endothelial growth factor receptor (VEGFR) inhibitors and are doing well and the total of 9 months has elapsed from start of invasive aspergillosis. There is no such case of invasive aspergillosis evidenced by literature until now due to pazopanib. This is the 1st time reported complication of invasive aspergillosis due to pazopanib treatment.

Among leukemic patients, three patients were B-cell acute lymphoblastic leukemia (ALL) and two were T-cell ALL. All leukemic patients developed invasive aspergillosis during reinduction phase BFM 95 moderate risk protocol treatment. All patients of leukemia were in critical neutropenia once IPA was diagnosed. All patients were on febrile neutropenia treatment on average of 10 days, with 4th generation cephalosporins, aminoglycosides and antistaph antibiotics, and oxygen inhalation. All these patients had an average temperature of 101°F and chest was the source of infection based on signs on chest examination. On evaluation, average absolute neutrophil count (ANC) was 100 cells/μL with total leukocyte count of 250 cells/μL, average platelet count 30,000/μL, average hemoglobin of 8.8 g/dL, ESR of 50 mm/first hour, normal kidney function tests, normal liver function tests, normal urine examination, sterile blood, and urine culture. CXR of three patients was normal and two patients had infiltrates localized in middle zones. ABG revealed PO_2 of 50 mmHg, PCO_2 of 35 mmHg with SpO_2 of 85%. Sputum examination and culture for fungus were normal in all patients. All patients subjected to HRCT chest, which revealed characteristic halo and crescent signs of invasive aspergillosis. Three patients had more than two spots and two had one lesion only. Diagnosis was further supported by galactomannan test and β-D-glucan assay. Blood was sent for same and an average value of 0.5 was taken as cut off, with maximum value of 2.0. On β-D-glucan assay, average value was 80 pg/mL with maximum of 180 pg/mL. Finally, patients were treated for IPA and patients became afebrile. Three patients who had multiple pulmonary aspergillosis spots on HRCT expired after a prolonged neutropenia of 1 month, two were B-cell, and one was T-cell leukemia patient. Hence, underlying disease and multiple lung involvement had bearing on over all prognosis of patient in IPA.

Among the two patients of multiple myeloma, both had stage IIIA disease and average age was 56.5 years and male:female ratio was 1:1. Both patients received dexamethasone-, bortezomib-, lenalidomide- and zoledronate-based treatment for 6 months followed by autologous stem cell transplant (AUST) with melphalan 200 mg/m^2 conditioning. While recovering from marrow suppression, they started with fever, cough, and shortness of breath with tachypnea and tachycardia. On evaluation, average hemoglobin of 8.0 g/dL, total leukocyte count of 500 cells/μL, neutrophil count of 200 cells/μL, platelet count of 7000/μL, and ESR of 75 mm/first hour were observed. Blood and urine cultures were sterile. ABG revealed PO_2 of 58 mmHg, PCO_2 of 33 mmHg. CXR revealed mid-zone infiltrates. Both patients were started on antistaph antibiotics, aminoglycosides and 4th generation cephalosporins and oxygen inhalation. This treatment was given for 10 days, but both patients persisted with symptoms. HRCT chest revealed characteristic halo and crescent signs of invasive aspergillosis. Both patients had one pulmonary lesion of invasive aspergillosis. Blood was sent for galactomannan test and an average value of 0.5 was taken as cut off, with maximum value of 1.6. On β-D-glucan assay, average value was 90 pg/mL with maximum of 170 pg/mL. Rest of investigations such as KFT, LFT, uric acid, and serum calcium were normal. Sputum for microscopic examination and culture came normal. Finally, both patients received injection voriconazole 6 mg/kg two doses 12 h apart followed by 4 mg/kg twice daily for 4 weeks followed by oral treatment for 6 months. Complete recovery was documented by repeating HRCT 6 months of treatment. Both patients are doing well and on lenalidomide maintenance for last 4 months.

Only one patient of carcinoma breast of stage IIIA with human epidermal growth factor receptor 2/neu positive, who got modified radical mastectomy and received adjuvant adriamycin/cyclophosphamide followed by taxol/trastuzumab combination. In middle of taxol/trastuzumab treatment, patient became febrile and had nonproductive cough. On evaluation, hemoglobin of 8.0 g/dL, total leukocyte count of 600 cells/μL, neutrophil count of 300 cells/μL, platelet count of 40,000/μL, and ESR of 45 mm/first hour were observed. Blood and urine cultures were sterile. ABG revealed PO_2 of 59 mmHg, PCO_2 of 38 mmHg. CXR revealed mid-zone infiltrates. She was started on antistaph antibiotics, aminoglycosides and 4th generation cephalosporins and oxygen inhalation. This treatment was given for 10 days, but both patients persisted with symptoms. Echocardiography was normal with EF of 70%. HRCT chest revealed characteristic halo and crescent signs of invasive aspergillosis. She had one pulmonary lesion of invasive aspergillosis. Blood was sent for galactomannan test and revealed a value of 2.0. On β-D-glucan assay, the value was 95 pg/mL. Rest of investigations such as KFT, LFT, uric acid, and serum calcium were normal. Sputum for microscopic examination and culture came normal. Finally, this patient received injection voriconazole 6 mg/kg two doses 12 h apart followed by 4 mg/kg twice daily for 4 weeks followed by oral treatment for 6 months. Complete recovery was documented by repeating HRCT at 6 months of treatment. The patient is still on trastuzumab maintenance and is doing well.

Since it is well known that immunosuppression due to HIV, high-dose chemotherapy, and prolonged steroid intake are risk factors for IPA, it was not known that VEGFR inhibitor (Pazopanib) therapy is a risk factor for IPA.

DISCUSSION AND REVIEW OF LITERATURE

Pulmonary disease is caused mainly by aspergillus fumigatus and has a spectrum of clinical syndromes. IPA is a severe disease and can be found not only in severely immunocompromised patients but also in critically ill patients and those with COPD. IPA was first described in 1953.[13] Due to widespread use of chemotherapy and immunosuppressive agents, its incidence has increased over the past two decades.[14,15] Of all autopsies performed between 1978 and 1992, the rate of invasive mycoses increased from 0.4% to 3.1% as documented by Groll *et al*.[16] IPA increased from 17% to 60% of all mycoses found on autopsy over the course of the study. The mortality rate of IPA exceeds 50% in neutropenic patients and reaches 90% in hematopoietic stem-cell transplantation (HSCT) recipients.[17,18] We studied IPA in immunocompromised hosts and found IPA in 6.6%. The mortality with IPA was seen in 30% patients.

The major risk factor for IPA is immunodeficiency, which includes neutropenia, HSCT and solid-organ transplantation, prolonged therapy with high-dose corticosteroids, hematological malignancy, cytotoxic therapy, advanced AIDS, and chronic granulomatous disease.[2,19-21] The most important risk factor is neutropenia, especially when there is an ANC <500 cells/mm^3. The risk of IPA correlates strongly with the duration and degree of neutropenia. The risk in neutropenic patients is estimated to increase by 1% per day for the first 3 weeks and then by 4% per day thereafter.[20] HSCT and solid-organ transplantation (especially lung transplantation) are also significant risk factors.[21,22] Several other factors predispose patients with transplantation to acquire IPA: Multiple immune defects including prolonged neutropenia in the preengraftment phase of HSCT; the use of multiple antirejection or antigraft versus host disease therapy (such as corticosteroids and cyclosporine); parenteral nutrition; use of multiple antibiotics; and prolonged hospitalization. In our study, we had immunocompromised patients either due to chemotherapy, steroids, high-dose chemotherapy, disease itself or pazopanib. Our median ANC was 250 and average neutropenia duration was 13 days, except in patients who were on pazopanib had ANC of 2000 for average duration of 2.5 months. In these two patients, IPA was independent of neutropenia and 1st time reported in literature. There has been a steady increase in the documented cases of IPA following HSCT where the risk is much higher following allogeneic rather than autologous HSCT (incidences of 2.3–15% and 0.5–4%, respectively).[18,23-26] In our study, 30 patients had undergone AUST for multiple myeloma and two (6.66%) patients developed IPA. All AUST recipients received posaconazole for prophylaxis except these two patients who received fluconazole prophylaxis. This further suggests that newer azoles have 100% efficacy in prevention of IPA if used in AUST recipient's prophylaxis.

Symptoms are nonspecific and usually mimic bronchopneumonia: Fever unresponsive to antibiotics, cough, sputum production, and dyspnea. Patients may also present with pleuritic chest pain (due to vascular invasion leading to thromboses that cause small pulmonary infarcts) and hemoptysis, which is usually mild but can be severe. IPA is one of the most common causes of hemoptysis in neutropenic patients and may be associated with cavitation that occurs with neutrophil recovery.[27] Our all patients presented with nonproductive cough, dyspnea, and fever; no patient had hemoptysis.

The diagnosis of IPA remains challenging. Early diagnosis of IPA in severely immunocompromised patients is difficult, and a high index of suspicion is necessary. The gold standard in the diagnosis of IPA is histopathological examination of lung tissue obtained by thoracoscopic or open-lung biopsy.[28] Isolation of an aspergillus species from sputum is highly predictive of invasive disease in immunocompromised patients. Studies have shown that sputum samples that are positive for aspergillus in patients with leukemia, or in those who have undergone HSCT, have a positive predictive value of 80–90%.[29-31] Conversely, negative sputum samples do not rule out IPA; negative sputum studies have been noted in 70% of patients with confirmed IPA.[31,32] Blood cultures are rarely positive in patients with confirmed IPA.[33] In our patient, series sputum and blood culture did not grow aspergillus fumigatus in any of the patients.

Chest radiography is of little use in the early stages of disease because the incidence of nonspecific changes is high. Usual findings include rounded densities, pleural-based infiltrates suggestive of pulmonary infarctions, and cavitations. Pleural effusions are uncommon.[34,35] Chest CT, especially when combined with high-resolution images (HRCT), is much more useful. The routine use of HRCT of the chest early in the course of IPA leads to earlier diagnosis and improved outcomes.[36,37] Typical chest CT scan findings in patients suspected to have IPA include multiple nodules and the halo sign, which is mainly seen in neutropenic patients early in the course of infection (usually in the 1st week) and appears as a zone of low attenuation due to hemorrhage surrounding the pulmonary nodule. Another late radiological sign is the air crescent sign, which appears as a crescent-shaped lucency in the region of the original nodule secondary to necrosis.[35,38] In our series, CXR was abnormal in 60 of patients with nonspecific infiltrates with one showed cavitation. HRCT chest revealed halo sign early and crescent sign latter, and one HRCT showed both findings together.

Bronchoscopy with BAL is generally helpful in the diagnosis of IPA, especially in patients with diffuse lung involvement. The sensitivity and specificity of a positive result of BAL fluid are about 50% and 97%, respectively, but this diagnostic yield of BAL in the diagnosis of IPA is not consistent, and much

lower yields have been reported.[29,30,39-43] However, BAL is still a safe and useful tool in high-risk patients suspected to have IPA. In addition to obtaining samples for fungal stain and culture, it may also be useful in detecting aspergillus antigens in the BAL fluid as well as excluding other infections. Transbronchial biopsies may be considered in selected patients. The most recent advances in the diagnosis of IPA are related to detecting aspergillus antigens in body fluids, mainly galactomannan and (13)-β-D-glucan (both are cellular wall constituents).

Galactomannan is a polysaccharide released by aspergillus during growth. A double-sandwich ELISA for the detection of galactomannan in serum is the best-characterized test and was approved by the US Food and Drug Administration for the diagnosis of IPA with a threshold of 0.5 ng/mL. It is reported that serum galactomannan can be detected several days before the presence of clinical signs, chest radiographic abnormalities, or a positive culture. Thus, galactomannan detection may allow earlier confirmation of the diagnosis; it may also assist in the assessment of the evolution of infection during treatment if serial serum galactomannan values are obtained.[44,45] Overall, the assay had a sensitivity of 71% and specificity of 89% for proven cases of IPA. The negative predictive value was 92–98% and the positive predictive value was 25–62%.[46] Pfeiffer *et al*.[46] also concluded that the galactomannan assay is more useful in patients who have a hematological malignancy or who have undergone allogeneic HSCT than in solid-organ transplant recipients or nonneutropenic patients. In our study, both galactomannan assay and β-D-glucan assay were used as adjunct to radiology for confirmation of IPA. These assays were done only if HRCT chest finding were highly suggestive of IPA. All patients were having positive galactomannan assay and β-D-glucan assay. The average value of serum galactomannan was 1.75 ng/mL (cut off 0.5) and average value of serum (13)-β-D-glucan was 180 ng/mL. These two adjunct tests were highly useful in confirming IPA patients in our setting who had positive HRCT chest. Sensitivity of both these assays was 100%. PCR is another way to diagnose IPA by the detection of aspergillus DNA in BAL fluid and serum. The sensitivity and specificity of PCR of BAL fluid samples are estimated to be 67–100% and 55–95%, respectively[47] while for serum samples, the sensitivity and specificity have been reported as 100% and 65–92%, respectively.[47-50]

A new broad-spectrum triazole, voriconazole, has been approved as the initial treatment of invasive aspergillosis and is currently considered the treatment of choice in many patients with IPA.[51-53] In a large prospective, randomized, multicenter trial, voriconazole was compared to amphotericin B as the primary therapy for IPA.[54] Patients receiving voriconazole had a higher favorable response rate at week 12 (53% *vs*. 32% in patients receiving amphotericin B) and a higher 12-week survival (71% *vs*. 58%). Voriconazole is available in both IV and oral formulations. The recommended dose is 6 mg/kg twice daily intravenously on day 1, followed by 4 mg/kg. Another broad-spectrum triazole, posaconazole, is very effective and safe as salvage therapy in patients with IPA refractory to standard antifungal therapy.[55-57] We also started patients on single agent voriconazole and combination of voriconazole and caspofungin in very sick ones. There was early expiry in 30% of patients because of prolonged neutropenia and IPA, all patients were leukemic. We observed 100% response at average of 4 months with either single drug or combination. Hence, overall response was 70% in our series which is consistent with literature.

Echinocandin derivatives such as caspofungin, micafungin, and anidulafungin are also effective agents in the treatment of IPA refractory to standard treatment, or if the patient cannot tolerate first-line agents.[58,59] While polyenes and azoles target the fungal cell membrane, echinocandins inhibit the (13)-β-D-glucan constituent of the fungal cell wall. Therefore, a combination antifungal therapy could be a strategy to treat refractory IPA.[60,61] There was survival advantage of voriconazole plus caspofungin compared with voriconazole alone was reported in one retrospective analysis of salvage therapy for IPA.[62] This combination was also compared with liposomal amphotericin B as primary therapy for IPA in solid organ transplant recipients in a prospective, multicenter, observational study.[63] The combination was associated with improved survival in subsets of recipients with renal failure. We also conclude to use combination in very sick patients at outset before we see refractoriness.

The treatment is often prolonged, lasting several months to 1-year prerequisites for discontinuing treatment include clinical and radiographic resolution, microbiological clearance, and reversal of immunosuppression. Reinstating therapy in patients who have responded should be considered if immunosuppression is resumed, or if the patient requires additional cytotoxic therapy or another HSCT. We gave treatment until 3 months and did interim assessment with HRCT, galactomannan assay, and (13)-β-D-glucan assay. All our survived patients had near normal HRCT chest and fungal assays were below cut off values. We further extended treatment for another 3 months. We did not get any relapse of IPA in any survived patient till last follow-up (average 6 months).

CONCLUSION

IPA is a difficult infection to treat in immucompromised state. It needs very high degree of suspicion to diagnose. Most of symptoms are nonspecific and HRCT chest is very important tool in its diagnosis. Other investigations adjunct to HRCT include galactomannan and (13)-β-D-glucan assay. Although Histo Patho Logical Examination (HPE) is important in definitive diagnosis, it is not mandatory in case of IPA. Newer VEGFR inhibitors were associated with IPA in our patients. Sick patients should be treated with

combination antifungal of different mechanisms at outset and therapy should be continued for 6 months. Interim assessment should be carried out by HRCT and newer galactomannan and (13)-β-D-glucan assay. In case of no responders to combination therapy, diagnosis should be revised and alternative diagnosis should be looked for.

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Conflicts of interest

There are no conflicts of interest.

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