Original Article

Feasibility and outcome of CT-guided lung biopsy in patients with hematological diseases and suspected fungal pneumonia

Sanjeev Kumar Sharma[1], Suman Kumar[1], Avinash Kumar Singh[1], Tulika Seth[1], Pravas Mishra[1], Manoranjan Mahapatra[1], Sanjay Sharma[2], Seema Tyagi[1], Immaculata Xess[3], Ruma Ray[4]

Departments of [1]Hematology, [2]Radiology, [3]Microbiology, [4]Pathology, All India Institute of Medical Sciences, New Delhi, India.

Abstract

Introduction: Fungal pneumonia is a major cause of morbidity and mortality in immunocompromised patients with hematological diseases. This study is aimed to evaluate the feasibility and outcome of computed tomography (CT) guided lung biopsy or fine needle aspiration cytology (FNAC) in the diagnosis of fungal pneumonia in patients with hematological diseases.

Methodology: Seven hundred and seventy six consecutive patients with febrile neutropenia were evaluated prospectively over the period of three years. Patients with suspected fungal pneumonia, based on typical CT scan findings, were considered for lung biopsy.

Results: Of the 776 patients evaluated for fever, 235 (30.3%) showed CT scan findings consistent with fungal pneumonia. Of the 235 patients, CT-guided lung biopsy/FNAC was recommended for 178 patients but could be performed in only 34 (19.1%) patients. Fungal pneumonia was proven in 15 (44%) out of 34 patients (aspergillus in 12; mucormycosis in 3 patients). Lung biopsies could not be performed for a number of reasons. These included thrombocytopenia, nodules being too small, infection improving with empiric treatment and patient recovering clinically, and the patient being too sick to undergo intervention. The median absolute neutrophil count (ANC) of patients at the time of lung biopsy was $0.41x10^9$/l in patients whose lung biopsy/FNAC showed fungal pneumonia, compared to $2.10x10^9$/l in patients whose biopsy/FNAC showed necrotizing pneumonitis.

Conclusion: CT-guided lung biopsy/FNAC can allow the definitive diagnosis of fungal pneumonia in selected patients with various hematological diseases and should be attempted whenever clinically indicated and radiologically feasible.

Key words: fungal pneumonia; immunocompromised patients; lung biopsy

J Infect Dev Ctries 2013; 7(10):748-752.doi:10.3855/jidc.2823

(Received 01 July 2012– Accepted 10 December 2012)

Introduction

The incidence of invasive fungal infections (IFI) in patients with hematological diseases is increasing as a consequence of high-dose chemotherapy and bone marrow transplant procedures, and is a major cause of morbidity and mortality. Moreover, treatment of fungal infections in such immunocompromised patients is especially costly in resource-poor and developing countries. Definitive treatment can be guided by tissue diagnosis, thereby avoiding empirical treatment in all patients. Though the diagnosis is often difficult, an early and accurate histopathological diagnosis is important for initiating treatment [1-5]. Aspergillosis frequently manifests as invasive pulmonary disease, accounting for 50-60% of all cases [2,5]. Proof of invasive aspergillosis requires either histology showing hyphae from fine needle aspiration cytology (FNAC), a biopsy with evidence of tissue damage, or a positive culture from a site that is normally sterile; otherwise, it is considered as a probable or possible infection [6]. Histological confirmation of the type of fungal infection, whether aspergillus or mucor, is important because mucor does not respond to azoles or echinocandins. CT-guided percutaneous lung biopsy/FNAC can help to distinguish these, allowing specific diagnosis and treatment [1-5]. This prospective study aimed to evaluate the feasibility of CT-guided lung biopsy/FNAC and the pattern of incidence of fungal infection in patients with hematological diseases admitted to the hematology wards of the All India Institute of Medical Sciences..

Methodology

This prospective study was conducted by the Department of Hematology in collaboration with the Departments of Radiology, Pathology and Microbiology, after approval from the ethics

committee of the institute. Seven hundred and seventy six consecutive patients with febrile neutropenia were evaluated prospectively over the period of three years, between July 2008 and August 2011. The tests routinely performed to evaluate febrile neutropenia included a complete hemogram with peripheral smears, liver and kidney function tests, and sputum, blood and urine cultures. Initial baseline chest radiographs were performed in all cases. Patients received treatment, including antibiotics and antifungals, per the standard of care for the management of febrile neutropenia in patients with hematological diseases. CT scans were performed as a part of the workup for febrile neutropenia. All CT scans were reviewed by a senior radiologist for evidence of fungal infection, which included the presence of nodule(s) and/or consolidations with or without ground glass opacities, a halo sign, and an air cresent sign. Inclusion criteria were immunocompromised patients with acute leukemia, lymphoma or aplastic anemia with a thoracic CT scan suggesting the focus of infection. Patients who were hemodynamically unstable and in whom platelet counts could not be maintained at over $50x10^9$/l inspite of platelet transfusions were excluded.

Patients were on antibacterial and empirical antifungal therapy at the time of their lung biopsies. Written informed consent was obtained prior to the procedure. Platelet count, prothrombin time (PT), and activated partial thromboplastin time (APTT) were determined one day before the procedure. Thrombocytopenic patients received platelet transfusions before the procedure, at the discretion of the clinical team, with the aim of maintaining a platelet count of more than $50x10^9$/l. CT-guided lung biopsy was performed by a radiologist in the CT suite. Decisions for patient positioning, aspiration versus biopsy, and the size of the needle required were made on a case-by-case basis by the radiologist, based on size and location of the lesion in the lungs. All procedures were performed under CT guidance using an 18-20 gauge coaxial biopsy needle after local anesthesia with 1% lidocaine. After the biopsy, patients were routinely observed for two hours, and chest radiographs were obtained to exclude complications, particularly pneumothorax.

Statistical analysis

The primary purpose of the study was to evaluate the feasibility of lung biopsy in patients with various haematological diseases. The secondary purposes were to determine the outcome in terms of yield, and to determine the complications related to the procedure. Statistical analysis included a t-test for assessing the difference in continuous values between the two groups; a chi-square test was used to assess the difference in categorical values between the two groups. A p-value < 0.05 was considered statistically significant..

Results

A total of 776 patients were evaluated for fever, and a CT scan was used to identify evidence for pneumonia (Table 1). Two hundred and thirty five patients (30.3%) showed CT scan evidence of fungal pneumonia, majority of whom had or were being treated for acute myeloid leukemia (AML) (36.08%), followed by acute lymphoblastic leukemia (24.6%) and aplastic anemia (20.8%).

Of the 235 patients with CT evidence of fungal pneumonia, CT-guided lung biopsy/FNAC was planned for 178 patients based on the size and location of the lesions, but it was feasible in only 34 (19.1%) patients; in 57 patients, intervention was not considered because nodules were too small or unfavorably located for a lung biopsy. Lesions located near major vessels, hilum, and lung fissures were generally avoided at the radiologist's discretion. Fifteen (44.1%) out of the 34 patients who underwent the biopsy/FNAC were found to have fungal pneumonia on histopathological examination of the specimen. The diagnostic yield (biopsy or FNAC showing fungus) was found to be 10/16 (62.5%) if the lesions were nodules, and 5/18 (27.7%) when the lesions were consolidations, though the type of lesion was not specific for predicting the outcome ($p = 0.15$). Ten (66.6%) out of the 15 patients with fungal pneumonia had ground-glass opacity (GGO) on the CT scan (Table 2), and out of the 19 patients who had necrotizing pneumonitis, five had GGO ($p = 0.04$, chi-square test). No significance was found when the delay in conducting the lung biopsy was compared with a positive yield (histopathological evidence of fungal pneumonia) versus a negative yield (biopsy showing necrotizing pneumonitis) ($p = 0.37$, t-test).

The median absolute neutrophil count (ANC) of patients at the time of the lung biopsy was $0.41x10^9$/l in patients whose lung biopsy/FNAC showed fungal pneumonia, compared to $2.10x10^9$/l in patients whose biopsy/FNAC showed necrotizing pneumonitis ($p < 0.001$, Mann Whitney test).

Three patients had mucormycosis; of these, two patients had aplastic anemia and one patient had AML.

Table 1. Distribution of patients according to hematological diseases, with suspected fungal pneumonia in each subgroup

Diseases	Number of patients	Suspected fungal infection (%)
Acute myeloid leukemia (AML)	280	101 (42.97)
Acute lymphoblastic leukemia (ALL)	191	59 (25.10)
Aplastic anemia (AA)	162	46 (19.57)
Acute promyelocytic leukemia (APML)	31	8 (3.40)
Myelodysplastic syndrome (MDS)	30	6 (2.55)
Chronic lymphocytic leukemia (CLL)	24	6 (2.55)
Multiple Myeloma (MM)	20	5 (2.12)
Non Hodgkins lymphoma (NHL)	19	2 (0.85)
Hairy cell leukemia (HCL)	11	2 (0.85)
Idiopathic myelofibrosis (IMF)	8	0
Total	776	235 (30.28)

Table 2. Comparison of yield in the two groups showing nodules or consolidations on CT scan

Biopsy results	Nodules (p<0.05)*	Consolidation (p<0.05)*
Fungal pneumonia (n=15)	10 (66.6%)	5 (33.3%)
Necrotizing pneumonitis (n=19)	6 (31.6%)	13 (68.4%)

*chi-square test

Table 3. Reasons for not being able to perform lung biopsy in patients with suspected fungal pneumonia

Reasons	Number of patients (n=144)
Thrombocytopenia not responding to platelet transfusion	75 (52.1%)
Patient too sick to undergo intervention	24 (16.6%)
Infection improved and patient recovered by the time CT biopsy was due	22 (15.3%)
Coagulopathy	12 (8.3%)
Consent not available for lung biopsy	11 (7.6%)

Two of the patients with mucormycosis were on empiric therapy with voriconazole, which was changed to amphotericin and resulted in complete recovery. The third patient, a case of aplastic anemia, developed mucormycosis following allogeneic peripheral blood stem cell transplantation. In 12 patients, Aspergillus was proven as the cause of pneumonia. The clinical manifestations in these patients varied from asymptomatic pulmonary nodules to large consolidations occluding major vessels. In 19 cases, the biopsy/FNAC showed necrotizing pneumonia probably due to either inadequate sampling where the biopsy missed the affected tissue or it had healed by the time biopsy was performed and only necrotic tissue remained. The median duration of the delay in performing a biopsy was 8.2 days (range 0-21), mostly because of thrombocytopenia. The most common complication related to CT-guided lung biopsy/FNAC was chest pain (11 patients). Three patients developed mild pneumothorax, and none required chest tube insertion. The reasons for not being able to perform interventions are listed in Table 3. Eight patients underwent a CT scan guided FNAC, as lesions were too small for biopsy, and the risk of complications was higher. Three of these eight patients showed fungal pneumonia (one patient had mucormycosis and two patients had aspergillus pneumonia).

Discussion

The incidence of IFI is increasing in patients with hematological diseases due to the use of high-dose chemotherapy and bone marrow transplant procedures [1,3,7]. Mortality is usually very high, particularly in patients with prolonged neutropenia [6,8]. The diagnosis is difficult in neutropenic patients because blood cultures are often negative and the diagnosis can only be characterized as probable. In these patients, a CT chest scan is very useful to identify probable pulmonary aspergillosis by detecting the presence of a halo sign or air crescent sign, which are characteristic of fungal infections [2,3]. As these patients also have severe thrombocytopenia, it may be necessary to wait for platelet counts to increase ($> 50x10^9$/l) before attempting invasive procedures. The Invasive Fungal Infection Cooperative Group of the EORTC and the Mycoses Study Group of the US National Institute of Allergy and Infectious Diseases (IFICG/MSG) require histopathological or cytopathological demonstration of hyphae with associated tissue damage, or a positive culture in a sample collected from a normally sterile site that is clinically or radiologically infected, as proof for invasive aspergillosis [6].

The feasibility of lung biopsies and the outcome of such interventions in 235 patients with suspected fungal pneumonia was evaluated at our institute. Only 34 (14.4%) patients could undergo the procedure. Of these patients, Aspergillus spp. was detected in 12 and mucormycosis was confirmed in 3 patients. This resulted in therapy change in two patients with mucormycosis who had been receiving voriconazole; a timely change to amphotericin resulted in a favourable outcome. Biopsies/FNACs in 19 patients did not reveal any pathogen. The diagnostic yield in this study was 44.1%. FNAC was performed in eight patients in whom the lesions were too small to be biopsied.

The median duration of delay in performing the procedure was 8.2 days (range 1-21 days), and the most common reason for delay was refractory thrombocytopenia. A delay in performing the lung biopsy did not have a significant effect on the yield (the result of a biopsied specimen), suggesting that interventions should be performed even if delayed because of the patient`s initial poor clinico-hematological condition. The median ANC of patients in whom biopsy revealed a fungus was significantly lower ($0.41x10^9$/l, range $0.20\text{-}1.40x10^9$/l) than in those patients whose biopsy showed necrotizing pneumonitis ($2.10x10^9$/l, range $0.24\text{-}4.62x10^9$/l) ($p < 0.001$), suggesting that yield is increased when ANC is lower, and with recovery of counts, the yield may decrease. Neutropenia is a risk factor for fungal pneumonia [6], and neutrophil recovery is associated with recovery from fungal pneumonia [9]. In a study by Nosari et al. [5], despite the delay (median of 15 days), the biopsy showed a diagnostic result in a large number of cases (76.4%), and allowed aspergillosis and mucormycosis to be discriminated. This histologic discrimination is very important because fungi of the mucorales order are usually resistant to azoles and echinocandins; only amphotericin B can be used for treatment of such cases. Unfortunately, radiologic signs alone are not able to discriminate between different fungal species [9,10]. Aspergillus is a common saprophyte; a positive culture from bronchalveolar lavage is not a proof of infection. Hence, the gold standard is mycologic and/or histologic evidence of tissue invasion. Mucormycosis infection is often underestimated because the clinical pictures of this infection and aspergillosis are similar.

A major advantage of lung biopsy/FNAC is that it provides an immediate diagnosis and usually does not have serious adverse effects. Pneumothorax and pulmonary hemorrhage, however, can occur. In the present study, there were no major complications related to the lung biopsy/FNAC. Small pneumothorax developed in three patients (8.8%) and did not require chest tube insertion. Eleven patients had chest pain related to the procedure, which was adequately controlled with analgesics. None of the patients had any bleeding complications. In a study by Shi et al. [3], the CT-guided lung biopsy was found to be an effective and safe method for the diagnosis of pulmonary fungal infection in patients with hematological diseases. Kallenberg et al. [4] also evaluated the diagnostic efficacy and safety of CT–guided transthoracic needle biopsy retrospectively in patients with hematologic malignancies, which led to changes in antimicrobial therapy for eight of the 22 (36.4%) patients, and was safe for patients with hematologic malignancies, causing minimal morbidity. Gupta et al. [11] also concluded that CT-guided lung biopsies provide a specific diagnosis in a majority of patients with hematologic malignancies, leading to therapeutic changes. With newer advances in diagnostic methods, various polymerase chain reaction-based molecular tests and antibody and antigen tests are being used for the diagnosis of IFI. The Galactomannan antigen test, which has a 90–100% specificity and 80–100% sensitivity in neutropenic patients is also being increasingly used [1].

Pneumonia remains a leading cause of death in immunocompromised patients with hematological diseases. As the lung biopsy is safe and effective in diagnosing the pathogen causing pneumonia, every attempt should be made to prove the fungal etiology in suspected cases [1,12]. In this prospective study, during follow-up of the patients who underwent lung biopsies, four patients with proven Aspergillus pneumonia died, and two deaths occurred in patients whose biopsies showed necrotizing pneumonitis. The causes of deaths were persistent neutropenia with sepsis in five cases, and leukemia relapse in one case. All three patients with mucormycosis recovered. Though a prospective study, the limitations of the present study included a small number of patients who could undergo biopsy, probably resulting in a low yield. Also, the galactomannan test was not used in this study

Conclusion

CT-guided lung biopsy seems to be a safe and effective procedure in patients with hematological diseases, if the coagulation parameters are normal or corrected prior to the procedure. Though the yield is less compared to the number of patients suspected of fungal pneumonia, it can differentiate aspergillosis from mucormycosis, and can guide specific therapy. A CT-guided biopsy should be considered, even if it has been delayed because of poor general condition or refractory thrombocytopenia..

Acknowledgements

We are thankful to Dr. Sandeep Kumar Sharma and Aashna Sharma for formatting the manuscript..

References

1. Ruhnke M, Böhme A, Buchheidt D, Cornely O, Donhuijsen K, Einsele H, Enzensberger R, Hebart H, Heussel CP, Horger M, Hof H, Karthaus M, Krüger W, Maschmeyer G, Penack O, Ritter J, Schwartz S (2012) Diagnosis of invasive fungal infections in hematology and oncology-guidelines from the Infectious Diseases Working Party in Hematology and Oncology of the German Society for Haematology and Oncology (AGIHO). Ann Oncol 23: 823-833.
2. Lass-Flörl C, Resch G, Nachbaur D, Mayr A, Gastl G, Auberger J, Bialek R, Freund MC (2007) The value of computed tomography-guided percutaneous lung biopsy for diagnosis of invasive fungal infection in immunocompromised patients. Clin Infect Dis 45: 101-104.
3. Shi JM, Cai Z, Huang H, Ye XJ, He JS, Xie WZ, Zhang J, Zhou XY, Luo Y, Lin Y, Li L, Zheng WY, Wei GQ, Lin MF (2009) Role of CT-guided percutaneous lung biopsy in diagnosis of pulmonary fungal infection in patients with hematologic diseases. Int J Hematol 89: 624–627.
4. Kallenberg MH, Gill RR, Factor RE, Bryar JM, Rubin RH, Jacobson FL, Marty FM (2009) Diagnostic efficacy and safety of computed tomography-guided transthoracic needle biopsy in patients with hematologic malignancies. AcadRadiol 16: 1408–1415.
5. Nosari A, Anghilieri M, Carrafiello G, Guffanti C, Marbello L, Montillo M, Muti G, Ribera S, Vanzulli A, Nichelatti M, Morra E (2003) Utility of percutaneous lung biopsy for diagnosing filamentous fungal infections in hematologic malignancies. Haematologica 88: 1405–1409.
6. Ascioglu S, Rex JH, De Pauw B, Bennett JE, Bille J, Crokaert F, Denning DW, Donnelly JP, Edwards JE, Erjavec Z, Fiere D, Lortholary O, Maertens J, Meis JF, Patterson TF, Ritter J, Selleslag D, Shah PM, Stevens DA, Walsh TJ (2002) Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an International Consensus. Clin Infect Dis 34: 7-14.
7. Kuhlman JE, Fishman EK, Burch PA, Karp JE, Zerhouni EA, Siegelman SS (1987) Invasive pulmonary aspergillosis in acute leukemia. The contribution of CT to early diagnosis and aggressive management. Chest 92: 95–99.
8. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP (2005) Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis 41: 60-66.
9. Milito MA, Kontoyiannis DP, Lewis RE, Liu P, Mawlawi OR, Truong MT, Marom EM (2010) Influence of host immunosuppression on CT findings in invasive pulmonary aspergillosis. Med Mycol 48: 817-823.
10. Pagano L, Offidani M, Fianchi L, Nosari A, Candoni A, Piccardi M, Corvatta L, Antonio D, Girmenia C, Martino P, Del Favero A (2004) Mucormycosis in hematologic patients. Haematologica 89: 207–214.
11. Gupta S, Sultenfuss M, Romaguera JE, Ensor J, Krishnamurthy S, Wallace MJ, Ahrar K, Madoff DC, Murthy R, Hicks ME (2010) CT-guided percutaneous lung biopsies in patients with haematologic malignancies and undiagnosed pulmonary lesions. HematolOncol 28: 75–81.
12. Prentice AG, Glasmacher A, Hobson RP, Schey S, Barnes RA, Donnelly JP, Jackson G (2007) Guidelines on the management of invasive fungal infection during therapy for haematological malignancy. British Committee for Standards in Haematology, London.

Corresponding author

Manoranjan Mahapatra, MD
Department of Hematology
All India Institute of Medical Sciences
New Delhi, India
Phone: 91-9868397235
Email: mrmahapatra@hotmail.com

Conflict of interests: No conflict of interests is declared.