Correlation Between CT Findings of Invasive Pulmonary Aspergillosis and Severity of Neutropenia

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ABSTRACT

Objective: The purpose of this study was to investigate the association between CT findings of invasive pulmonary aspergillosis and neutrophils level.

Methods: This retrospective study included the patients diagnosed with invasive pulmonary aspergillosis by computed tomography (CT) at Siriraj Hospital (Bangkok, Thailand) during May 2006 to May 2010. The patients were classified into two groups: group I = neutrophils <500 cells/mm^3, and group II = neutrophils ≥500 cells/mm^3. Patient demographic and clinical data were collected. CT findings were compared between groups, including consolidation, pulmonary nodule, pulmonary mass, centrilobular nodule, CT halo sign, CT hypodense, air crescent, central cavity, lymphadenopathy, and pleural effusion.

Results: Of the 43 patients that were included, 14 patients were assigned to group I, and 29 patients were allocated to group II. The mean age of patients was 40.2 years, and 48.8% were male. The most common CT finding of invasive pulmonary aspergillosis was pulmonary nodules (83.7%), followed by CT halo sign (76.7%) and consolidation (69.7%). The CT finding that showed significantly more commonly in patients in group I and group II was consolidation (p=0.02) and central cavity (p=0.03), respectively.

Conclusion: Consolidation was the CT finding significantly most commonly observed in invasive pulmonary aspergillosis with neutrophils <500 cell/mm^3, and central cavity was the finding significantly most commonly found in patients with neutrophils ≥500 cell/mm^3 with non-specific distribution.

Keywords: Aspergillosis; neutropenia; CT scan; lung; pulmonary (Siriraj Med J 2019; 71: 385-391)

INTRODUCTION

Aspergillus spp. are filamentous fungi that are acquired via the inhalation of spores. Pulmonary aspergillosis has 4 types, including allergic bronchopulmonary aspergillosis (ABPA), aspergilloma, semi-invasive pulmonary aspergillosis, and invasive pulmonary aspergillosis. Each type of pulmonary aspergillosis depends on host immunity.[1,2] Invasive pulmonary aspergillosis is a major complication in immunocompromised patients. Major risk factors for invasive pulmonary aspergillosis infection include prolonged neutropenia (<500 cells/mm^3 for >10 days) or neutrophil dysfunction, post-transplantation, prolonged (>3 weeks) and high-dose corticosteroid therapy, hematological malignancy (e.g., leukemia), cytotoxic therapy, and advanced AIDS.[1,3]

Neutrophils are the dominant host defense against fungi by their action as natural killer cells that are recruited to the lungs by chemokines. They aggregate around conidia in the airways to prevent their germination.[4,5] Neutropenia for more than 10 days is the most important risk for invasive pulmonary aspergillosis. In addition, invasive pulmonary aspergillosis is related to the duration and

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degree of neutropenia. The risk of invasive pulmonary aspergillosis in neutropenic patients was estimated to be 1% per day for the first 3 weeks.[1]

Diagnosis of invasive pulmonary aspergillosis is made by clinical findings, physical examination, laboratory markers (polymerase chain reaction, galactomannan testing), sputum or bronchoalveolar lavage fluid culture, histopathology, and radiologic findings. The clinical presentation of invasive pulmonary aspergillosis is usually non-specific, such as fever, clinical unresponsive to antibiotics, chest pain, hemoptysis, and productive cough.[6,7] Early diagnosis of invasive pulmonary aspergillosis is necessary in these patients because the outcome depends on early treatment with an appropriate antifungal drug. Computed tomography (CT) chest imaging is an important diagnostic tool for early diagnosis.[8]

Chest radiograph is not sufficiently sensitive for the diagnosis of invasive pulmonary aspergillosis. Plain chest radiograph may exhibit non-specific nodular opacities or air-space infiltration in early phase. However, the air crescent sign and cavitation may become visible on chest radiographs in later stage.[2,6]

Thoracic CT scan is the most sensitive investigation for early detection of invasive pulmonary aspergillosis. Thoracic CT should be performed in neutropenic patients with fever that are not responding to antibiotics.[6] The gold standard investigation for diagnosis of invasive pulmonary aspergillosis is histological or pathological examination of lung tissue from needle aspiration or biopsy. However, these procedures are invasive, and they are associated with an increased risk of bleeding. As a result, thoracic CT scan is considered to be much more useful method for early diagnosis, and it has a prognostic impact on the outcome by detection of early disease.

CT findings of invasive pulmonary aspergillosis are variable. Findings that might be observed include CT halo sign (consisting of a central nodule, mass, or consolidation surrounded by a zone of hemorrhage that is found in the early phase of disease), crescentation or central cavity sign (develops days to weeks after the initial presentation, or in the resolving phase of the infection when neutropenia in the peripheral blood is increasing), CT hypodense sign (consisting of central low-density area within nodule or consolidation caused by vascular obstruction with secondary lung infarction), and non-specific nodular opacities or air space infiltration in the early stage of infection.[2,8,9]

The aim of this study was to identify association between thoracic CT findings of invasive pulmonary aspergillosis and serum neutrophil level.

MATERIALS AND METHODS

Subjects

All patients aged greater than 15 years with diagnosis of invasive pulmonary aspergillosis who underwent thin-section thoracic CT scan at the Division of Diagnostic Radiology, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during May 2006 to May 2010 were retrospectively reviewed. Patients diagnosed with proven, probable, or possible invasive pulmonary aspergillosis according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group were included.[3] The protocol for this study was approved by the Siriraj Institutional Review Board (Si 180/2011).

Serum neutrophil level and clinical data (age, underlying diseases, presenting symptoms, laboratory investigation, time interval from clinical onset to CT findings, and histological or pathological report) of all individuals were collected from our center's electronic medical record database. Regarding serum neutrophil level, patients were classified into either group I (neutrophils <500 cells/mm^3) or group II (neutrophils ≥500 cells/mm^3).

Imaging and imaging interpretation

CT examinations were obtained with a 64-slice multi-detector row CT (GE or Siemens). The GE parameters were 120 kVp, 250 mA, and pitch = 1.375 craniocaudal, and the Siemens parameters were 120 kVp, 250 mA, and pitch = 0.8 craniocaudal. Spiral CT scan was obtained during full inspiration with or without contrast media administration.

The CT findings were assessed by two radiologists, and conclusions were reached by consensus. The pattern of pulmonary abnormality findings, associated findings, and distribution was analyzed. The pulmonary abnormality findings were consolidation (area of increase in pulmonary parenchymal attenuation that obscures the margin of vessels and airway wall), pulmonary nodule (round opacity lesion, ≤3 cm in diameter), pulmonary mass (round pulmonary opacity >3 cm in diameter), and centrilobular nodule (small opacity in the center of a secondary pulmonary lobule).[10] The associated findings were "CT halo sign" (ground-glass attenuation surrounding a pulmonary nodule or consolidation) (Fig 1), CT hypodense sign (the differences between lung opacity in the peripheral zone of the lesion and lower density of necrotic central area >15 HU in mediastinal window setting) (Fig 2), air

crescent sign (crescent shaped area of air density within pulmonary nodule or mass) (Fig 3), central cavity (a lucent area of air density within an area of consolidation, nodule, or mass) (Fig 4), lymphadenopathy, and pleural effusion.[8]

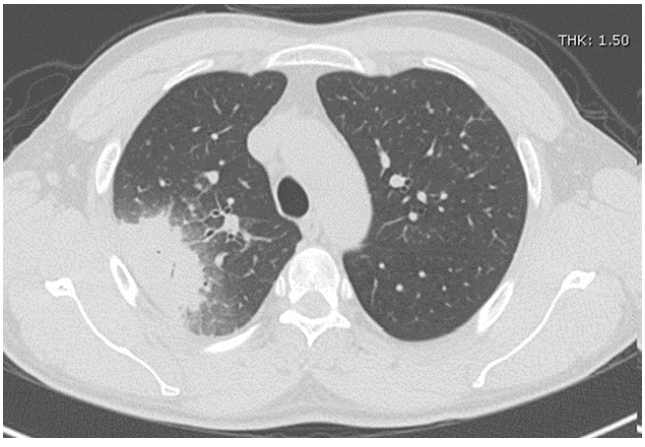

Fig 1. A 40-year-old male with underlying acute aplastic anemia and neutrophils 28 cells/mm^3 presented with fever and cough. Axial thoracic CT scan demonstrated pulmonary consolidation surrounded with ground-glass opacity at right upper lobe that represented CT halo sign. The final diagnosis was invasive pulmonary aspergillosis.

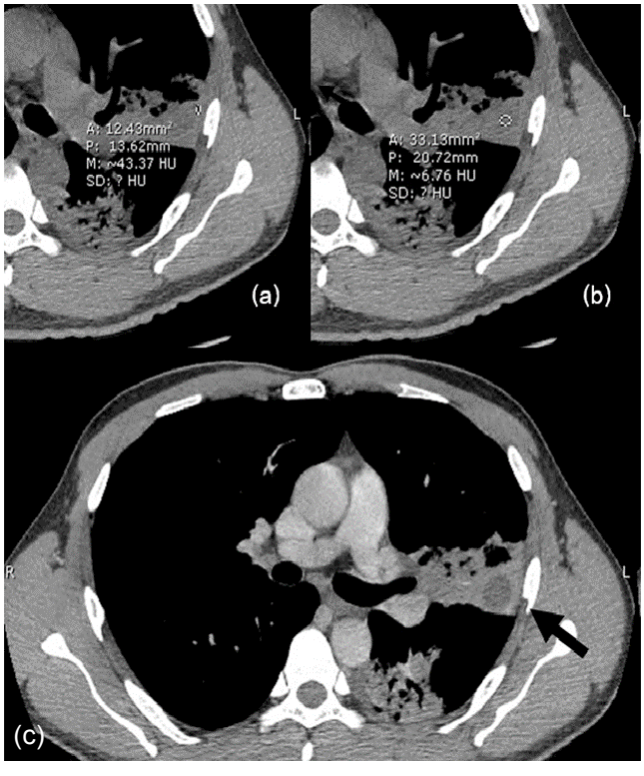

Fig 2. A 32-year-old male with underlying acute myeloblastic leukemia and neutrophils 1,761 cells/mm^3 presented with fever. (a, b) axial unenhanced thoracic CT scan demonstrated two consolidation areas at left upper lobe. One of them showed differences in lung opacity in the peripheral zone of the lesion (43.3 HU in a), and lower density of necrotic central areas (6.7 HU in b) that represented CT hypodense sign. (c) axial post-contrast-enhanced thoracic CT confirmed CT hypodense sign (arrow). The final diagnosis was invasive pulmonary aspergillosis.

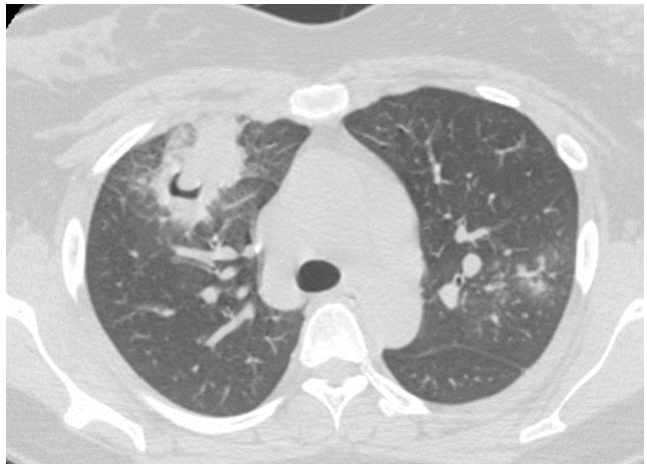

Fig 3. A 27-year-old female with underlying acute myeloblastic leukemia and neutrophils 3,171 cells/mm^3 presented with fever. Axial thoracic CT scan demonstrated a crescent shaped area within an area of consolidation that represented air crescent sign at right upper lobe. Ground-glass nodules at left upper lobe were also noted. The final diagnosis was invasive pulmonary aspergillosis.

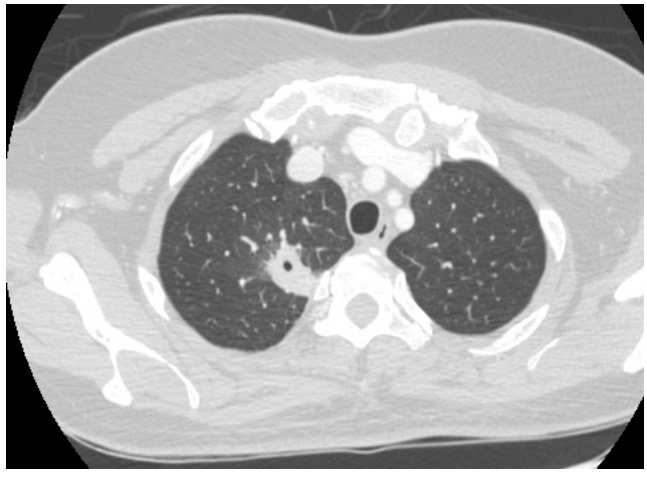

Fig 4. A 53-year-old male with underlying acute myeloblastic leukemia and neutrophils 1,159 cells/mm^3 with history of fever and cough. Axial thoracic CT scan demonstrated a lucent area within nodule that represented central cavity at right upper lobe. The final diagnosis was invasive pulmonary aspergillosis.

Statistical analysis

The age of patients and duration from imaging to CBC examination are expressed as mean. All qualitative data, including gender, different criteria for diagnosis of invasive pulmonary aspergillosis, and CT findings, are described as frequency and percentage. Chi-square test was used to analyze the radiographic findings, and to examine for correlation between 2 groups of CT findings and neutrophil levels. A *p*-value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using a statistical software package (SPSS Statistics version 13.0; SPSS, Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

The characteristics of 43 patients with diagnosis of invasive pulmonary aspergillosis by proven (6.9%), probable (20.9%), and possible (72.0%) criteria are summarized in Table 1. Patients were classified into 2 groups. Fourteen patients (32.6%) were classified in group I (serum neutrophil level <500 cell/mm^3), and 29 patients (67.4%) were classified in group II (serum neutrophil level ≥500 cell/mm^3). The mean age of patients in group I (40.7 years) was not significantly different from that of group II (39.9 years). The gender distribution was similar in each of the 2 groups (group I: 7 males and 7 females vs. group II: 14 males and 15 females). The mean time interval from the date of thoracic CT scan to CBC was 0.7 days in group I, and 0.6 days in group II (p>0.05). The mean time interval from clinical onset to CT findings was 9.9 days in group I, and 13.2 days in group II (p>0.05). The underlying diseases in group I were aplastic anemia (21.4%), acute lymphoblastic leukemia (21.4%), acute myeloid leukemia (35.7%), chronic myeloid leukemia (14.3%), and unspecified neutropenia (7.1%). The underlying diseases in group II were acute lymphoblastic leukemia (20.7%), acute myeloid leukemia (58.6%), chronic myeloid leukemia (3.4%), lymphoma (13.8%), and systemic lupus erythematosus (3.4%).

CT protocol

There were 38 CT studies (87.7%) performed with contrast medium administration, and 5 studies (12.3%) performed without contrast medium administration. Regarding slice thickness of the CT scan, 0.6 mm was used in 5 studies (10.8%), 0.63 mm in 7 studies (16.9%), 1.25 mm in 16 studies (36.9%), 1.5 mm in 13 studies (30.8%), and 4 mm in 2 studies (4.6%).

Imaging interpretation

CT findings of invasive pulmonary aspergillosis and associated findings were assessed for the following radiological patterns; consolidation, pulmonary nodule, pulmonary mass, centrilobular nodule, CT halo sign, CT hypodense sign, air crescent, central cavity, lymphadenopathy, and pleural effusion. The prevalence of each of these finding was compared between groups (Table 2).

TABLE 1. Patient demographic and clinical characteristics.

Characteristics	Neutrophils <500 cells/mm^3	Neutrophils ≥500 cells/mm^3	Total
Number, n (%)	14 (32.6%)	29 (67.4%)	(N=43)
Age (mean)	40.7 years	39.9 years	40.2 years
Gender, n (%)			
Male	7	14	21 (48.8%)
Female	7	15	22 (51.2%)
Criteria diagnosis, n (%)			
Proven IPA	1 (7.1%)	2 (6.9%)	3 (7.0%)
Probable IPA	4 (28.6%)	5 (17.2%)	9 (20.9%)
Possible IPA	9 (64.3%)	22 (75.9%)	31 (72.1%)
Duration from imaging to CBC (mean)	0.7 days	0.6 days	0.7 days
Underlying conditions, n (%)			
Aplastic anemia	3 (21.4%)	0 (0.0%)	3 (7.0%)
ALL	3 (21.4%)	6 (20.7%)	9 (20.9%)
AML	5 (35.7%)	17 (58.6%)	22 (51.2%)
CML	2 (14.3%)	1 (3.4%)	3 (7.0%)
Lymphoma	0 (0.0%)	4 (13.8%)	4 (9.3%)
SLE	0 (0.0%)	1 (3.4%)	1 (2.3%)
Unspecified neutropenia	1 (7.1%)	0 (0.0%)	1 (2.3%)

Abbreviations: IPA=invasive pulmonary aspergillosis; CBC=complete blood count; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; CML=chronic myeloid leukemia, SLE=systemic lupus erythematosus

TABLE 2. Computed tomography (CT) findings and associated findings of invasive pulmonary aspergillosis compared between neutrophil levels.

CT findings	Neutrophils <500 cells/mm³	Neutrophils ≥500 cells/mm³	Total	P-value
Consolidation	13 (92.9%)	17 (58.6%)	30 (69.7%)	0.02
Nodule	11 (78.6%)	25 (86.2%)	36 (83.7%)	0.52
Mass	0 (0.0%)	1 (3.4%)	1 (2.3%)	0.48
Centrilobular nodule	1 (7.1%)	2 (6.9%)	3 (6.9%)	0.97
Associated findings	**Neutrophils <500 cells/mm³**	**Neutrophils ≥500 cells/mm³**	**Total**	**P-value**
Peripheral GGO (halo sign)	13 (69.9%)	20 (69.0%)	33 (76.7%)	0.08
CT hypodense sign	5 (35.7%)	13 (44.8%)	18 (41.8%)	0.57
Air crescent sign	1 (7.1%)	8 (27.6%)	9 (37.2%)	0.12
Central cavity	2 (14.3%)	14 (48.3%)	16 (37.2%)	0.03
Lymphadenopathy	3 (11.5%)	4 (13.8%)	7 (16.2%)	0.96
Pleural effusion	10 (71.4%)	12 (41.4%)	22 (51.1%)	0.06

A *p*-value <0.05 indicates statistical significance
Abbreviation: GGO=ground glass opacification

There was no significant difference in the pattern of pulmonary nodule (78.6% in group I vs. 86.2% in group II, *p*=0.52), pulmonary mass (0% in group I vs. 3.4% in group II, *p*=0.48), centrilobular nodule (7.1% in group I vs. 6.9% in group II, *p*=0.97), CT halo sign (69.9% in group I vs. 69.0% in group II, *p*=0.08), CT hypodense sign (35.7% in group I vs. 44.8% in group II, *p*=0.57), air crescent sign (7.1% in group I vs. 27.6% in group II, *p*=0.12), lymphadenopathy (11.5% in group I vs. 13.8% in group II, *p*=0.96) and pleural effusion (71.4% in group I vs. 41.4% in group II, *p*=0.96), as shown in Table 2.

Consolidation was the CT finding significantly more commonly found in group I than in group II (92.9% vs. 58.6%, respectively; *p*=0.02). Central cavity was the CT finding significantly more commonly observed in group II than in group I (48.3% vs. 14.3%, respectively; *p*=0.03).

The distribution of lesions was, as follows: right upper lobe (RUL) (83.7%), left upper lobe (LUL) (72.1%), right lower lobe (RLL) (69.8%), left lower lobe (LLL) (67.4%), and right middle lobe (RML) (48.8%).

DISCUSSION

Invasive pulmonary aspergillosis is a major cause of mortality in immunocompromised patients. Neutrophils and alveolar macrophages play important roles in killing conidia and developing hyphae. If abnormalities exist in these defense mechanisms, the conidia undergo germination and turn to invasive hyphae. As such, neutropenia status is a major risk factor for invasive pulmonary aspergillosis.[2,5] The clinical signs and symptoms of invasive pulmonary aspergillosis include fever, unresponsiveness to antibiotics, productive cough, dyspnea, haemoptysis, and pleuritic chest pain. Diagnosis of invasive pulmonary aspergillosis can be made by combining clinical, radiographic, laboratory, and histopathologic data. Thoracic CT scan has become an important tool for diagnosing invasive pulmonary aspergillosis due its non-invasive nature and its high sensitivity (>80%) and specificity (60-98%).[6]

Pathologically, Aspergillus spp. invades pulmonary blood vessels and cause hemorrhagic infarction. Characteristic early lesions consist of central areas of necrosis surrounded by a zone of hemorrhage, which

corresponds with the CT halo sign.[11,12] The process of cavitation characteristically results in the air crescent sign, which histologically represents necrotic lung mixed with hyphae and granulocytic infiltrate that is surrounded by a thin rim of air.[2,11,13]

Hyung Jin Won, *et al.* described CT findings in 5 patients with neutropenia (<500 cells/mm^3) and proven invasive pulmonary aspergillosis. Most common manifestation of invasive pulmonary aspergillosis was segmental area of consolidation with ground-glass appearance (i.e., CT halo sign) (n=4, 20%) and at least one nodule surrounded by a halo (n=2, 40%).[9] Kuhlman, *et al.* found the typical CT findings of invasive pulmonary aspergillosis to be multiple nodules or fluffy masses or consolidation with surrounding halos of low attenuation. Some form of cavitation or air crescent formation was found at or near the time of granulocyte recovery.[12] Horger, *et al.* found the CT hypodense sign in 13 of 43 patients (30.2%) with invasive pulmonary aspergillosis. Eleven patients (84.6%) had neutrophils <500 cells/mm^3 and 2 patients (15.4%) had neutrophils ≥500 cells/mm^3, and the CT hypodense sign was more common in patients with neutrophils <500 cells/mm^3. The CT hypodense sign showed an area of central necrosis and proved to be a precursor of the crescent sign within a range of 2-19 days.[8] Logan, *et al.* assessed the CT findings and pathological findings in invasive aspergillosis of the airways in 9 patients. Their result showed CT findings in patients with neutrophil level <500 cells/mm^3 (n=3) to be peribronchial consolidation, CT halo sign, and centrilobular micronodules. The CT findings in patients with neutrophil level ≥500 cells/mm^3 (n=6) were centrilobular micronodules, diffuse bronchiectasis, peribronchial consolidation, and diffuse ground-glass attenuation.[14] However, no previous study reported significant difference in the CT findings of invasive pulmonary aspergillosis patients compared between those with neutrophil level <500 cells/mm^3 and those with neutrophil level ≥500 cells/mm^3.

The present study found the most common CT finding of invasive pulmonary aspergillosis to be pulmonary nodules, followed by CT halo sign and consolidation. We classified patients into 2 groups (group I = neutrophil level <500 cells/mm^3, and group II = neutrophil level ≥500 cells/mm^3) and compared findings between groups. We found consolidation to be significantly more commonly observed in patients with neutrophil level <500 cell/mm^3. This is because the extent and severity of infection in patients depends on the degree of immunodeficiency and duration of neutropenia.[2] Invading fungi are more expanded in individuals with profound granulocytopenia, which results in a greater extent of infected infarction (consolidation). Central cavity was found significantly more often in patients with neutrophil level ≥500 cells/mm^3. This might be explained by the cavitating process of fungal nodules, which relies on granulocytic response. Fungal nodules in patients with granulocytic function defect or in patients who remain neutropenic do not cavitate.[2,15]

The most common CT finding of invasive pulmonary aspergillosis in the present study was presence of pulmonary nodule (36 of 43 cases [83.7%]), and the second most common finding was CT halo sign (33 of 43 cases [76.7%]). However, neither of these findings were statistically significantly different between groups. The other CT findings that showed no significant difference between groups were centrilobular nodule, pleural effusion, pulmonary mass, CT hypodense sign, air crescent sign, and lymphadenopathy. These lesions in this study showed no obvious prominence in any pulmonary lobes, which indicates non-specific distribution.

Limitations

This study has some mentionable limitations. First, the retrospective nature of our study made it difficult to control factors, such as CT protocol (with or without contrast, slice thickness) and duration from date of CT scan to date of CBC examination. Second, there were only 3 proven cases of invasive pulmonary aspergillosis by histology or cytopathology. This can be explained by the fact needle aspiration and lung biopsy are both invasive procedures that are associated with increased risk of bleeding in patients with a hematologic problem. Third, the size of our study population was relatively small and there was substantial asymmetry between groups. It is possible that these factors could have adversely influenced the results of our statistical analyses.

CONCLUSION

Consolidation was the CT finding significantly most commonly observed in invasive pulmonary aspergillosis with neutrophils <500 cell/mm^3, and central cavity was the finding significantly most commonly found in patients with neutrophils ≥500 cell/mm^3 with non-specific distribution.

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