Original Article
Pulmonary invasive fungal disease and bacterial pneumonia: a comparative study with high-resolution CT

Wei Chen1*, Xuanqi Xiong1*, Bin Xie1, Yuan Ou1, Wenjing Hou1, Mingshan Du1, Yongling Chen1, Kang Chen1, Jing Li1, Li Pei2, Gang Fu2, Dingyuan Liu2, Ying Huang3

Departments of 1Radiology, 2Hematology, 3Respiratory Medicine, Southwest Hospital, Third Military Medical University, Chongqing 400038, China. *Equal contributors.

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Abstract: Background: Early diagnosis of invasive fungal disease (IFD) is challenging. High-resolution computed tomography (CT) may improve IFD diagnosis; however, there are no definitive imaging signs for differentiating between bacterial pneumonia and IFD. Methods: We retrospectively evaluated CT images of 208 patients with IFD (n = 102) or bacterial pneumonia (n = 106). We classified pulmonary opacities as consolidations, ground-glass opacities (GGOs), or nodules and recorded the presence of perinodular ground-glass halos, reversed halo sign (RSH), and cavitation (crescent-shaped or not). Results: Consolidation appeared in 83.3% and 92.5% of patients with IFD and bacterial pneumonia, respectively. Multifocal non-segmental consolidation was more common in IFD (48%) than bacterial pneumonia (22.6%; P < 0.05). Segmental or subsegmental consolidation was more common in bacterial pneumonia (43.4%) than IFD (7.8%; P < 0.01). GGOs and nodules were more common in IFD than bacterial pneumonia (60.8% vs. 24.5% and 54.9% vs. 15.1%, respectively; each P < 0.05). Consolidation combined with GGO, nodules, or both GGO and nodules was more frequent in IFD than in bacterial pneumonia (each P < 0.05). Nodules with halo sign (n = 23) appeared in 22.5% and 3.8% of patients with IFD and bacterial pneumonia, respectively. Nodules with RSH appeared only in IFD, and those with cavitation appeared in 11.8% and 1.9% of patients with IFD and bacterial pneumonia, respectively. Conclusions: Consolidation plus GGO and nodules or consolidation plus nodules is suggestive for IFD. Segmental or subsegmental consolidations are more frequent in bacterial pneumonia than in IFD. Large nodules, as well as nodules with halo sign or both small and large nodules, are related to IFD.

Keywords: Invasive fungal disease, bacterial pneumonia, high-resolution computed tomography

Introduction

Invasive fungal disease (IFD) of the lung is a common complication in immunocompromised patients and is associated with high morbidity and mortality [1]. Early diagnosis of IFD is often difficult, but it is imperative to improve patient survival. Serum galactomannan testing may have a role in diagnosis, but it has low sensitivity and frequent false-positive results [2-4]. Computed tomography (CT) plays an important role in the diagnosis and management of patients with fungal infections due to its ability to reveal early predictive signs of fungal infection [5-8]. In recognition of advances in diagnostic technology, a consensus committee of the European Organization for Research and Treatment of Cancer (EORTC) Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Disease Mycoses Study Group (MSG) updated the guidelines for IFD classification [9]. The updated guidelines include an increased role for CT scans. CT is probably the most important tool for the management of early IFD and may be superior to the mycological criteria established by the EORTC/MSG [6, 7, 10]. However, pulmonary CT findings are nonspecific. The diagnostic sensitivity of the radiologic criteria specified by the EORTC/MSG definition of invasive aspergillosis is low compared with the gold standard of autopsy examination [11]. Several studies have focused on describing specific CT signs of pulmonary aspergillosis [6, 12, 13], but there is little information about CT features that may allow IFD to be distinguished from bacterial pneumonia. The aim of this study was to distinguish the CT features of IFD from those of bacterial pneumonia to improve the early diagnosis of IFD.
Table 1. CT findings of pulmonary infections

<table>
<thead>
<tr>
<th>CT findings</th>
<th>Classification</th>
<th>IFD (n = 102)</th>
<th>Bacterial pneumonia (n = 106)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation</td>
<td></td>
<td>85 (83.3)</td>
<td>98 (92.5)</td>
<td></td>
</tr>
<tr>
<td>Shape</td>
<td>Non-segmental focal</td>
<td>14 (13.7)</td>
<td>15 (14.2)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Non-segmental multifocal</td>
<td>49 (48)</td>
<td>24 (22.6)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>Segmental or subsegmental</td>
<td>8 (7.8)</td>
<td>46 (43.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Segmental + non-segmental</td>
<td>14 (13.7)</td>
<td>13 (12.3)</td>
<td></td>
</tr>
<tr>
<td>With cavitation (including air crescent sign)</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reversed halo sign</td>
<td></td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGO</td>
<td></td>
<td>62 (60.8)</td>
<td>26 (24.5)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Diffuse</td>
<td></td>
<td>26 (25.4)</td>
<td>8 (7.5)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Patchy</td>
<td></td>
<td>36 (35.2)</td>
<td>18 (16.9)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Nodules</td>
<td></td>
<td>63 (61.8)</td>
<td>23 (21.7)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Size</td>
<td>Small</td>
<td>15 (14.7)</td>
<td>14 (13.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>20 (19.6)</td>
<td>3 (2.8)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Both small and large</td>
<td>28 (27.5)</td>
<td>6 (5.7)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Tree-in-bud</td>
<td></td>
<td>12 (11.8)</td>
<td>9 (8.5)</td>
<td></td>
</tr>
<tr>
<td>Halo</td>
<td></td>
<td>23 (22.5)</td>
<td>4 (3.8)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>With cavitation (incl. air crescent sign)</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td></td>
<td>21 (20.6)</td>
<td>52 (49.1)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Data are given as the number (percentage) of patients. *Calculated using the Fisher exact test. IFD: invasive fungal disease, GGO: ground-glass opacity.

Materials and methods

Patient population

This study is a retrospective evaluation of 208 consecutive patients diagnosed with IFD or bacterial pneumonia between October 2014 and September 2015. The 102 patients with IFD included 55 females and 47 males, with a mean age of 43.6 (range 22-65) years. The 106 patients with bacterial pneumonia included 43 females and 63 males, with a mean age of 47.9 (range 19-67) years. All of the patients with IFD had a proven or probable diagnosis of IFD according to the consensus EORTC/MSG criteria [9]. Proven IFD was defined by histological evidence of tissue invasion. Probable IFD was defined by the presence of host factors; clinical findings such as a halo sign, air-crescent sign, or cavity within an area of consolidation on CT; and mycological evidence of fungal infection from culture, cytological analysis of bronchoalveolar lavage (BAL) fluid, or galactomannan measurement in the serum or BAL. Confirmation of IFD patients consisted of a positive culture of BAL fluid and associated radiologic findings. Diagnosis of bacterial pneumonia was based on a positive culture of sputum or bronchoscopic aspirate in addition to positive blood or pleural fluid cultures. CT scans were performed when IFD or bacterial pneumonia was clinically suspected. According to the regulations of the Ethics Committee of Southwest Hospital, informed consent was not necessary for this retrospective study.

Computed tomography

CT examinations were performed using a dual-source CT scanner (Somatom Definition, Siemens, Erlangen, Germany). The scanning parameters for the chest CT were 120 kVp, 120 mAs, 1.25 mm collimation, pitch of 1, and routine 512 × 512 matrix. Clinical images were reconstructed with 5-mm-thick axial images (width 1200 HU, centered on a density of -600 HU) and 2-mm-thick axial images using high spatial frequency algorithm intervals with a sharp kernel (B46). All patients were scanned in the supine position from the lung apex to the base of the chest during full inspiration. In most cases, no intravenous contrast was applied.
Image analysis

Lung lesions were interpreted on a (picture archiving and communication system (PACS). Three radiologists, each with 10-15 years of experience in the interpretation of thoracic CT examinations (C.W., C.Y.L., and C.P.), analyzed the CT scans and made decisions about the pattern, distribution, and extent of pulmonary abnormalities by means of consensus. We classified the pattern as consolidation, ground-glass opacity (GGO), nodules, or a combination of two or more of those findings [14]. Consolidation and nodules were defined as areas of dense increase in attenuation, with obscuration of the underlying vessels. We further subcategorized consolidation as segmental or non-segmental and as patchy or focal. We defined patchy consolidation as a wedge-shaped area with shape and size corresponding to a secondary pulmonary lobule or subsegment. We defined GGO as a hazy increase in lung attenuation without obscuration of the underlying pulmonary vasculature. A nodule was defined as an area with well or poorly defined, rounded opacity that was no greater than 3 cm. We defined nodules < 1 cm in diameter as small and those > 1 cm in diameter as large. We defined halo sign as an area of GGO surrounding a nodule. We used the term “tree-in-bud pattern” to describe centrilobular branching structures that resembled a budding tree. A cavity was defined as a gas-filled space, visible as a lucency within a pulmonary lesion, and air crescents surrounding soft-tissue lesions to constitute a crescent sign.

Statistical analysis

Statistical analysis was performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Fisher exact probability and Chi-square tests were used to determine the statistical significance of differences in the presence of CT features between patient groups. P-values < 0.05 were considered statistically significant.

Results

The frequencies of the different features of parenchymal involvement in IFD and bacterial pneumonia are summarized in Table 1. There was no significant difference in the frequency of consolidation between bacterial pneumonia (93 of 106 patients, 62.3%) and IFD (85 of 102 patients, 83.3%). In IFD, the consolidation was focal and non-segmental in 14 patients (13.7%), multifocal and non-segmental in 49 patients (48%), segmental or subsegmental in 8 patients (7.8%), and both segmental and non-segmental in 14 patients (13.7%). In bacterial pneumonia, the consolidation was focal and non-segmental in 10 patients (9%), multifocal and non-segmental in 24 patients (22.6%), segmental or subsegmental in 46 patients (43.4%), and both segmental and non-segmental in 13 patients (12.3%; Figure 1). Non-segmental consolidation was more common in IFD than in bacterial pneumonia (48% vs. 22.6%; P < 0.05). Segmental or subsegmental consolidation was more common in bacterial pneumonia than in IFD (43.4% vs. 7.8%; P < 0.01).

GGO was more common in IFD than in bacterial pneumonia (60.8% vs. 24.5%; P < 0.05). Both patchy and diffuse GGO distributions were more common in patients with IFD than in those with bacterial pneumonia (each P < 0.05; Table 1).

Nodules were more common in IFD than in bacterial pneumonia (60.8% vs. 16.9%; P < 0.05). Furthermore, both large nodules and mixtures of small and large nodules were more common in IFD than in bacterial pneumonia (19.6% vs. 0.9% and 27.5% vs. 5.7%, respectively; each P < 0.001). There was no significant difference in the frequency of tree-in-bud opacities between the two diseases. Six patients with IFD had nodules with cavitation, whereas no patients with bacterial pneumonia had them.

In terms of combinations of consolidation, GGO, and nodules, consolidation alone was less common in IFD than in bacterial pneumonia (25 of 85 patients, 24.5%) and IFD (14 of 35 patients, 13.2%; P < 0.05). Consolidation + GGO was more common in IFD than in bacterial pneumonia (27 of 85 patients, 26.5%) and IFD (12 of 35 patients, 11.3%; P < 0.05). Consolidation + nodules was more common in IFD than in bacterial pneumonia (27 of 85 patients, 28.5%) and IFD (12 of 35 patients, 11.3%; P < 0.05). Consolidation + nodules + GGO was more common in IFD than in bacterial pneumonia (23 of 85 patients, 26.5%) and IFD (6 of 35 patients, 7.8%; P < 0.05). GGO + nodules was more common in IFD than in bacterial pneumonia (10 of 85 patients, 11.8%) and IFD (3 of 35 patients, 5.7%; P < 0.05).

Table 1. Combinations of CT features of pulmonary infections

<table>
<thead>
<tr>
<th>CT pattern</th>
<th>IFD (n = 85)</th>
<th>Bacterial pneumonia (n = 35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation + GGO</td>
<td>25 (24.5)</td>
<td>14 (13.2)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Consolidation + nodules</td>
<td>27 (26.5)</td>
<td>12 (11.3)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Consolidation + nodules + GGO</td>
<td>23 (22.5)</td>
<td>6 (5.7)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>GGO + nodules</td>
<td>10 (9.8)</td>
<td>3 (2.8)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Data are given as the number (percentage) of patients unless otherwise indicated. Percentages may not equal 100% because of rounding. IFD: invasive fungal disease, GGO: ground-glass opacity.
HRCT of IFD and bacterial pneumonia

common in IFD than in bacterial pneumonia (9.8% vs. 62.3%; P < 0.01; Figure 1). Among the patients with IFD, four (3.9%) had only GGO, and three (2.1%) had only nodules. Similarly, among the patients with bacterial pneumonia, three (2.8%) had only GGO, and two (1.8%) had only nodules. The remaining 85 patients with IFD and 40 patients with bacterial pneumonia had various combinations of consolidation, GGO, and nodules (Table 2). There were several combinations that appeared more frequently in IFD than in bacterial pneumonia: consolidation plus GGO (24.5% vs. 13.2%, P < 0.05; Figure 2), at least one segmental area of consolidation plus at least one nodule (26.4% vs. 11.3%, P < 0.05; Figures 3 and 4), GGO plus at least one nodule (9.8% vs. 2.8%, P < 0.05; Figure 5), and at least one segmental area of consolidation plus GGO and at least one nodule 22.5% vs. 5.7%, P < 0.01; Figures 6-8).

The halo sign appeared in 22.5% of the patients with IFD and 3.8% of the patients with bacterial pneumonia (P < 0.05). The reversed halo sign (RHS) appeared in 7.8% of the patients with IFD and none of the patients with bacterial pneumonia. The tree-in-bud pattern appeared in 11.8% of the patients with IFD and in 8.5% of the patients with bacterial pneumonia. Cavitation appeared in 9.8% of the patients with IFD (Figure 2) and only 1.9% of the patients with bacterial pneumonia (Table 1).

Discussion

Mortality rates from IFD are exceedingly high among immunocompromised patients. Early diagnosis of IFD followed by anti-fungal therapy is expected to improve those outcomes. Empiric therapy is usually started as soon as there is clinical suspicion of fungal infection; however, antifungal drugs are expensive and can have severe side effects. CT signs of IFD have been shown to precede serum galactomannan positivity [10]. In a previous study, a CT-based treatment strategy for IFD in immunocompromised patients seemed feasible, and a CT-based preemptive strategy reduced the use of parenteral antifungal agents by 68% [18]. Those results highlight the importance of early diagnosis and treatment in IFD. In practice, the most challenging task is to differentiate between bacterial pneumonia and IFD.

The clinical and radiological manifestations of pulmonary IFD have been studied extensively and are well known [15-20]. The revised EORTC/
HRCT of IFD and bacterial pneumonia

MSG criteria extended the guidelines for the radiological diagnosis of IFD [9], but there are still no definitive, highly specific imaging signs for early recognition. In our study, 22.5% of the patients with IFD presented with dense, well-circumscribed lesions (nodules) accompanied by a halo sign, thus meeting the radiological criteria for IFD as defined by the EORTC/MSG. The halo sign is neither sensitive nor specific for IFD, however, and is occasionally present in patients with other diseases [22-25]. Our radiological findings in patients with IFD consisted mostly of ill-defined consolidations, nodules, and ground-glass infiltrates. IFD often presents as a nonspecific air-space consolidation. Christe et al. reported that wedge-shaped, pleural-based consolidations were indicative of pulmonary IFD with a specificity of 100% and a

Figure 4. CT pattern of consolidation + nodules, High-resolution CT scans of a 46-year-old man with myelodysplastic syndrome. A: A consolidation area with air bronchogram in the right upper pulmonary lobe (arrow) due to IFD. B: An irregular nodular appearance in the left lower lobe (arrowhead) due to IFD.

Figure 5. CT pattern of GGO + nodules High-resolution CT scans of a 51-year-old man with non-Hodgkin’s lymphoma. A-D: Diffuse, bilateral, ill-defined nodular opacities with a tree-in-bud appearance, multiple large nodules (arrowhead), and patchy ground-glass attenuation in the right upper lobe (yellow arrows) due to IFD.
sensitivity of 43-46% [26]. However, other studies showed a low sensitivity (25%) of wedge-shaped consolidation for IFD diagnosis [21]. Extensive vascular permeation and apparent occlusion of small-to-medium-sized arteries by fungal hyphae, with or without thrombus formation, are suggestive of pulmonary aspergillosis [12]. In contrast, the presence of lobar or segmental consolidation areas suggests bacterial pneumonia [27, 28]. In our series, three out of 102 patients with IFD presented wedge-shaped consolidations, which may not be helpful in early diagnosis. The late appearance of wedge-shaped consolidations during the course of pulmonary IFD limits its usefulness for early diagnosis.
Consolidation was the most common CT finding in both IFD and bacterial pneumonia in our study. There was no significant difference in the overall frequency of that finding between the two diseases; however, 62.3% of the patients with bacterial pneumonia exhibited segmental or subsegmental consolidation without GGO or nodules. In contrast, multifocal, non-segmental consolidation occurred significantly more often in patients with IFD than in those with bacterial pneumonia. Therefore, segmental or subsegmental consolidation is suggestive of bacterial pneumonia [26, 29], whereas multifocal non-segmental consolidation suggests IFD [4, 12, 17].

The EORTC/MSG consensus recently showed confidence in the etiologic significance of morphologic features of pulmonary opacities, defining any new occurrence of halo sign, cavitation, or air-crescent sign as a major criterion for fungal infection [9]. Nevertheless, some authors are skeptical about the possibility of CT-based etiologic diagnosis of pulmonary infections in immunocompromised patients [27, 30]. The results of our study suggest that some CT patterns are clinically significant in distinguishing IFD from bacterial pneumonia.

Specific CT patterns that differentiate IFD from other pulmonary infections would be very useful in the early diagnosis of IFD. The CT patterns of segmental consolidation plus GGO and nodules, or segmental consolidation plus nodules, occurred significantly more often in IFD than in bacterial pneumonia, and thus appear to have a high predictive value for IFD. In our series, the halo sign was present in 22.5% of the patients with IFD but only 3.8% of those with bacterial pneumonia. The RHS has been reported in association with other infectious conditions and some non-infectious processes [31, 32]. It was initially described as a relatively specific finding in the diagnosis of cryptogenic organizing pneumonia [7, 33], but it was subsequently reported in a wide spectrum of diseases including infectious and non-infectious conditions [34-36]. The RHS lesion differs from the pattern of necrosis and cavitation. Legouge reported that the presence of the RHS on CT was a strong indicator of pulmonary mucormycosis in leukemic patients with neutropenia [37, 38]. In our study, eight out of 102 patients with IFD exhibited a typical RHS, but none of the patients with bacterial pneumonia exhibited that sign. Hence, we suggest that the RHS could be added to the list of diagnostic CT findings of
HRCT of IFD and bacterial pneumonia

IFD. Cavitation or air-crescent formation occurs later in the course of the disease and is considered highly suggestive of IFD [39]; however, the sensitivity of those signs in IFD diagnosis did not exceed 27% in previous studies [38]. We observed nodules with cavitation in six patients with IFD but not in any patients with bacterial pneumonia.

Our study has some limitations. The number of patients was small, and we did not perform lung biopsies. Our inclusion criteria could also have caused a selection bias. Another limitation was the lack of comparison with other pulmonary infections.

Conclusion

Our results show that a CT pattern of either segmental consolidation plus GGO and nodules or segmental consolidation plus nodules can be considered suggestive of IFD. Segmental or subsegmental consolidation appeared more frequently in bacterial pneumonia than in IFD. Large nodules, nodules with a halo sign, or both small and large nodules were associated with IFD. Those results suggest that CT scan can be useful for the early differential diagnosis of IFD.

Disclosure of conflict of interest

None.

Address correspondence to: Dingyuan Liu and Ying Huang, Department of Respiratory Medicine, Southwest Hospital, Third Military Medical University, Chongqing 400038, China. Tel: +86 23 68754721; Fax: +86 23 65463026; E-mail: ldy20001@163.com (DYL); hga_83@sina.com (YH)

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HRCT of IFD and bacterial pneumonia


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